1. SUMMARY AND CONCLUSIONS

1.1. BACKGROUND

Tobacco smoking has long been recognized (e.g., U.S. DHEW, 1964) as a major cause of mortality and morbidity, responsible for an estimated 434,000 deaths per year in the United States (CDC, 1991a). Tobacco use is known to cause cancer at various sites, in particular the lung (U.S. DHHS, 1982; IARC, 1986). Smoking can also cause respiratory diseases (U.S. DHHS, 1984, 1989) and is a major risk factor for heart disease (U.S. DHHS, 1983). In recent years there has been concern that nonsmokers may also be at risk for some of these health effects as a result of their exposure ("passive smoking") to the tobacco smoke that occurs in various environments occupied by smokers. Although this environmental tobacco smoke (ETS) is dilute compared to the mainstream smoke (MS) inhaled by active smokers, it is chemically similar, containing many of the same carcinogenic and toxic agents.

In 1986, the National Research Council (NRC) and the Surgeon General of the U.S. Public Health Service independently assessed the health effects of exposure to ETS (NRC, 1986; U.S. DHHS, 1986). Both of the 1986 reports conclude that ETS can cause lung cancer in adult nonsmokers and that children of parents who smoke have increased frequency of respiratory symptoms and acute lower respiratory tract infections, as well as evidence of reduced lung function.

More recent epidemiologic studies of the potential associations between ETS and lung cancer in nonsmoking adults and between ETS and noncancer respiratory effects more than double the size of the database available for analysis from that of the 1986 reports. This U.S. EPA document critically reviews the current database on the respiratory health effects of passive smoking, and these data are utilized to develop a hazard identification for ETS and to make quantitative estimates of the public health impacts of ETS for lung cancer and various other respiratory diseases.

The weight-of-evidence analysis for the lung cancer hazard identification is developed in accordance with U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a) and established principles for evaluating epidemiologic studies. The analysis considers animal bioassays and genotoxicity studies, as well as biological measurements of human uptake of tobacco smoke components and epidemiologic data on active and passive smoking. The availability of abundant and consistent human data, and especially human data at actual environmental levels of exposure to the specific agent (mixture) of concern, allow a hazard identification to be made with

25010317 58

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

a high degree of certainty. The conclusive evidence of the dose-related lung carcinogenicity of MS in active smokers (Chapter 4), coupled with information on the chemical similarities of MS and ETS and evidence of ETS uptake in nonsmokers (Chapter 3), is sufficient by itself to establish ETS as a known human lung carcinogen, or "Group A" carcinogen under U.S. EPA's carcinogen classification system. In addition, this document concludes that the overall results of 30 epidemiologic studies on lung cancer and passive smoking (Chapter 3), using spousal smoking as a surrogate of ETS exposure for female never-smokers, similarly justify a Group A classification.

The weight-of-evidence analyses for the noncancer respiratory effects are based primarily on a review of epidemiologic studies (Chapter 7). Most of the endpoints examined are respiratory disorders in children, where parental smoking is used as a surrogate of ETS exposure. For the noncancer respiratory effects in nonsmoking adults, most studies used spousal smoking as an exposure surrogate. A causal association was concluded to exist for a number of respiratory disorders where there was sufficient consistent evidence for a biologically-plausible association with ETS that could not be explained by bias, confounding, or chance. The fact that the database consists of human evidence from actual environmental exposure levels gives a high degree of confidence in this conclusion. Where there was suggestive but inconclusive evidence of causality, as was the case for asthma induction in children, ETS was concluded to be a risk factor for that endpoint. Where data were inconsistent or inadequate for evaluation of an association, as for acute upper respiratory tract infections and acute middle ear infections in children, no conclusions were drawn.

This report has also attempted to provide estimates of the extent of the public health impact, where appropriate, in terms of numbers of ETS-attributable cases in nonsmoking subpopulations. Unlike for qualitative hazard identification assessments where information from many sources adds to the confidence in a weight-of-evidence conclusion, for quantitative risk assessments the usefulness of studies usually depends on how closely the study population resembles nonsmoking segments of the general population. For lung cancer estimates among U.S. nonsmokers, the substantial epidemiology database of ETS and lung cancer among U.S. female never-smokers was considered to provide the most appropriate information. From the large number of similarly designed studies, pooled relative risk estimates were calculated and used in the derivation of the population risk estimates. The large number of studies available, the generally consistent results, and the condition of actual environmental levels of exposure increase the confidence in these estimates. Even with these conditions, however, uncertainties remain, such as in the use of questionnaires and current biomarker measurements to estimate past

250103175

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

exposure, assumptions of exposure-response linearity, and extrapolation to male never-smokers and to exsmokers. Still, given the strength of the evidence for the lung carcinogenicity of tobacco smoke and the extensive human database from actual environmental exposure levels, fewer assumptions are necessary than is usual in U.S. EPA quantitative risk assessments and confidence in these estimates is rated medium to high.

Population estimates of ETS health impacts are also made for certain noncancer respiratory endpoints in children, specifically lower respiratory tract infections (LRIs, i.e. pneumonia, bronchitis, and bronchiolitis) and episodes and severity of attacks of asthma. Estimates of ETS-attributable cases of LRI in infants and young children are thought to have a high degree of confidence because of the consistent study findings and the appropriateness of parental smoking as a surrogate measure of exposure in very young children. Estimates of the number of asthmatic children whose condition is aggravated by exposure to ETS are less certain than those for LRIs because of different measures of outcome in various studies and because of increased extraparental exposure to ETS in older children. Estimates of the number of new cases of asthma in previously asymptomatic children also have less confidence because at this time the weight-of-evidence for asthma induction, while suggestive of a causal association, is not conclusive.

Most of the ETS population impact estimates are presented in terms of ranges, which are thought to reflect reasonable assumptions about the estimates of parameters and variables required for the extrapolation models. The validity of the ranges is also dependent on the appropriateness of the extrapolation models themselves.

While this report focuses only on the respiratory health effects of passive smoking, there may also be other health effects of concern. Recent analyses of more than a dozen epidemiology and toxicology studies (Steenland, 1992; NIOSH, 1991) suggest that ETS exposure may be a risk factor for cardiovascular disease. In addition, there were a few studies in the literature linking ETS exposure to cancers of others sites; at this time, that database appears inadequate for any conclusion. This report does not develop an analysis of either the nonrespiratory cancer or the heart disease data and takes no position on whether ETS is a risk factor for these diseases. If it is, the total public health impact from ETS will be greater than that discussed here.

2501031760

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

1.2. PRIMARY FINDINGS

A. Lung Cancer in Nonsmoking Adults

1. Passive smoking is causally associated with lung cancer in adults, and ETS, by the total weight-of-evidence, belongs in the category of compounds classified by EPA as Group A (known human) carcinogens.
2. An estimated range of 2,500 to 3,300 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States. The confidence in this range is medium to high with approximately 3,000 annual lung cancer deaths representing the best estimate.

B. Noncancer Respiratory Diseases and Disorders

1. Exposure of children to ETS from parental smoking is causally associated with:
   a. increased prevalence of respiratory symptoms of irritation (cough, sputum, and wheeze),
   b. increased prevalence of middle ear effusion (a sign of middle ear disease), and
   c. a small but statistically significant reduction in lung function as tested by objective measures of lung capacity.
2. ETS exposure of young children and particularly infants from parental (and especially mother's) smoking is causally associated with an increased risk of lower respiratory tract infections (pneumonia, bronchitis, and bronchiolitis). This report estimates that exposure to ETS contributes 150,000 to 300,000 lower respiratory tract infections annually in infants and children less than 18 months of age, resulting in 7,500 to 15,000 hospitalizations. These higher risks continue at a decreasing rate for children until about age 3, but no estimates are derived for children over 18 months.
3. a. Exposure to ETS is causally associated with additional episodes and increased severity of asthma in children who already have the disease. This report estimates that ETS exposure exacerbates symptoms in approximately 20% of this country's 2 million to 5 million asthmatic children and is a major aggravating factor in approximately 10%.

2501031761

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

b. In addition, the epidemiologic evidence is suggestive but not conclusive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms. Based on this evidence and the known ETS effects on both the immune system and lungs (e.g. atopy and airway hyperresponsiveness), this report concludes that ETS is a risk factor for the induction of asthma in previously asymptomatic children. Data suggest that relatively high levels of exposure are required to induce new cases of asthma in children. This report estimates that previously asymptomatic children exposed to ETS from mothers who smoke at least 10 cigarettes per day will exhibit a probable range of 8,000 to 26,000 new cases of asthma annually. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

4. Passive smoking has subtle but significant effects on the respiratory health of nonsmoking adults, including coughing, phlegm, chest discomfort, and reduced lung function.

This report also has reviewed data on the relationship of maternal smoking and sudden infant death syndrome (SIDS), which is thought to involve some unknown respiratory pathogenesis. The report concludes that while there is strong evidence that infants whose mothers smoke are at an increased risk of dying from SIDS, available studies do not allow us to differentiate whether and to what extent this increase is related to in utero versus postnatal exposure to tobacco smoke products. Consequently, at this time this report is unable to assert whether or not ETS exposure by itself is a risk factor for SIDS independent of smoking during pregnancy. Postnatal exposure may potentiate effects of in utero tobacco smoke exposure, or it may not have any additional effect.

Regarding an association of parental smoking with either upper respiratory tract infections (colds and sore throats) or acute middle ear infections in children, this report finds the evidence inconclusive.

1.2.1. ETS and Lung Cancer

The Surgeon General (U.S. DHHS, 1989) estimated that smoking was responsible for more than one of every six deaths in the United States and that it accounted for about 90% of the lung cancer deaths in males and about 80% in females in 1985. Smokers, however, are not the only

05/31/92
2501031762

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

ones exposed to tobacco smoke. The sidestream smoke (SS) emitted from a smoldering cigarette between puffs (the main component of ETS) has been documented to contain many of the same carcinogenic compounds (known and suspected human and animal carcinogens) that have been identified in the mainstream smoke (MS) inhaled by smokers. Exposure concentrations of these carcinogens to passive smokers are variable but much lower than for active smokers. An excess cancer risk from passive smoking, however, is biologically plausible.

Based on the firmly established causal association of lung cancer with active smoking with a dose-response relationship down to low doses (Chapter 4), passive smoking is considered likely to affect the lung similarly. The widespread presence of ETS in both home and workplace and its absorption by nonsmokers in the general population have been well documented by air sampling and by body measurement of biomarkers such as nicotine and cotinine (Chapter 3). This raises the question of whether any direct evidence exists for the relationship between ETS exposure and lung cancer in the general population and what its implications may be for public health. This report addresses that question by reviewing and analyzing the evidence from 30 epidemiologic studies of effects from normally occurring environmental levels of ETS (Chapter 5). Because there is widespread exposure and it is difficult to construct a truly unexposed subgroup of the general population, these studies compare individuals with higher ETS exposure to those with lower exposures. Typically, female never-smokers who are married to a smoker are compared with female never-smokers who are married to a nonsmoker. Some studies also consider ETS exposure of other subjects (i.e., male never-smokers and long-term former smokers of either sex) and from other sources (e.g., workplace and home exposure during childhood), but these studies are fewer and represent fewer cases, and they are generally excluded from the analysis presented here. Use of the female never-smoker studies provides the largest, most homogeneous database for analysis to determine whether an ETS effect on lung cancer is present. This document assumes that the results for female never-smokers are generalizable to all nonsmokers.

Given that ETS exposures are at actual environmental levels and that the comparison groups are both exposed to appreciable background (i.e., nonspousal) ETS, any excess risk for lung cancer from exposure to spousal smoke would be expected to be small. Furthermore, the risk of lung cancer is relatively low in nonsmokers, and most studies have a small sample size, resulting in a very low statistical power (probability of detecting a real effect if it exists). Besides small sample size and low incremental exposures, other problems inherent in several of the studies may also limit their ability to detect a possible effect. Therefore, this document examines the data in several different ways. After downward adjustment of the relative risks for smoker

250103176 3

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

misclassification bias, the studies are individually assessed for strength of association and exposure-response trend. Then the study results are pooled by country using statistical techniques for combining data, including both positive and nonpositive results, to increase the ability to determine whether or not there is an association between ETS and lung cancer. Finally, in addition to the previous statistical analyses that weigh the studies only by size, regardless of design and conduct, the studies are qualitatively evaluated for potential confounding, bias, and likely utility to provide information about any lung carcinogenicity of ETS. Based on these qualitative considerations, the studies are categorized into one of four tiers and then statistically analyzed successively by tier.

Results from all of the analyses described above strongly support a causal association between lung cancer and ETS exposure. The overall proportion of individual studies found to show an association between lung cancer and ETS exposure is unlikely to occur by chance ($p < 0.005$). Similarly, the proportion showing a statistically significant dose-response trend ($p < 10^{-9}$) is highly supportive of a causal association. Combined results by country showed statistically significant associations for Greece (2 studies), Hong Kong (4 studies), Japan (5 studies), and the United States (11 studies), and in that order of strength of relative risk. Pooled results of the four Western European studies (three countries) actually showed a slightly stronger association than that of the United States, but it was not statistically significant, probably due to the smaller sample size. The combined results of the Chinese studies do not show an association between ETS and lung cancer; however, two of the four Chinese studies were designed mainly to determine the lung cancer effects of high levels of other indoor air pollutants indigenous to those areas, which would obscure a smaller ETS effect. These two Chinese studies do, however, provide very strong evidence on the lung carcinogenicity of these other indoor air pollutants, which contain many of the same components as ETS. When results are combined only for the other two Chinese studies, they demonstrate a statistically significant association for ETS and lung cancer.

The relative risks for Greece and Japan of 2.00 and 1.44, respectively, are probably the best estimates, because both female smoking prevalence and nontobacco-related lung cancer risks, which tend to dilute the estimates of ETS effects, are low in these two countries. Also, for the time period for which ETS exposure was of interest, spousal smoking is considered to be a better surrogate for ETS exposure in these societies than in Western countries, where other sources of ETS exposure (work, public places, and other nonhome environments) are generally higher.

2501031764

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Based on these analyses and following the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight-of-evidence, principally:

- Biological plausibility. ETS is taken up by the lungs, and components are distributed throughout the body. The presence of the same carcinogens in ETS and mainstream smoke, along with the established causal relationship between lung cancer and active smoking with the dose-response relationships exhibited down to low doses, make it reasonable to conclude that ETS is also a lung carcinogen.
- Supporting evidence from animal bioassays and genotoxicity experiments. The carcinogenicity of tobacco smoke has been established in lifetime inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of ETS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments. Positive results of genotoxicity testing for both MS and ETS provide corroborative evidence for their carcinogenic potential.
- Consistency of response. All 4 of the cohort studies and 20 of the 26 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as exposed to ETS. Of the 17 studies judged to be of higher utility based on study design, execution, and analysis (Appendices A and C), 15 observed higher risks, and 6 of these increases were statistically significant, despite most having low statistical power. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.
- Broad-based evidence. These 26 case-control and 4 prospective studies provide data from 8 different countries, employ a wide variety of study designs and protocols, and are conducted by many different research teams. Results from all countries, with the possible exception of two areas of China where high levels of other indoor air lung carcinogens were present, show small to modest increases in lung cancer associated with spousal ETS exposure. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.

2501031765

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

- Upward trend in dose-response. Both the largest of the cohort studies, the Japanese study of Hirayama--200 lung cancer cases, and the largest of the case-control studies, the U.S. study by Fontham and associates (1991)--420 lung cancer cases and two sets of controls, demonstrate a strong dose-related statistical association between passive smoking and lung cancer. This upward trend is well supported by the preponderance of epidemiology studies. Of the total of 17 studies in which data are classified by exposure level, 11 were statistically significant for the trend despite most having low statistical power.
- Detectable association at environmental exposure levels. Within the population of married women who are lifelong nonsmokers, the excess lung cancer risk from exposure to their smoking husbands' ETS is large enough to be observed. Carcinogenic responses are usually detectable only in high-exposure circumstances, such as occupational settings, or in experimental animals receiving very high doses. In addition, effects are harder to observe when there is substantial background exposure in the comparison groups, as is the case here.
- Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk for ETS exposure. The evidence remains statistically significant and conclusive, however, after adjustments for smoker misclassification. For the United States, the summary estimate of relative risk from nine case-control plus two cohort studies is 1.19 (90% confidence interval [C.I.] = 1.04-1.35) after adjustment for misclassification ($p < 0.05$). For Greece, 2.00 (1.42, 2.83), Hong Kong, 1.61 (1.25, 2.06) and Japan, 1.44 (1.13, 1.85), the estimated relative risks are higher than those of the United States and more highly significant after adjusting for the potential bias.
- Confounding cannot explain the association. The broad-based evidence for an association found by independent investigators across several countries, as well as the positive dose-response trends observed in most of the studies that analyzed for them, make any single confounder highly unlikely as an explanation for the results. In addition, this report examined potential confounding factors (history of lung disease, home heat sources, diet, occupation) and concluded that none of these factors could account for the observed association between lung cancer and ETS.

2501031766

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The individual risk of lung cancer from exposure to ETS does not have to be very large to translate into a significant health hazard to the U.S. population because of the large number of smokers and the widespread presence of ETS. Current smokers comprise approximately 26% of the U.S. adult population and consume more than one-half trillion cigarettes annually (1.5 packs per day, on average), causing nearly universal exposure to at least some ETS. As a biomarker of tobacco smoke uptake, cotinine, a metabolite of the tobacco-specific compound nicotine, is detectable in the blood, saliva, and urine of persons recently exposed to tobacco smoke. Cotinine has typically been detected in 50% to 75% of reported nonsmokers tested (50% equates to 63 million U.S. nonsmokers of age 18 or above).

The best estimate of approximately 3,000 lung cancer deaths per year in U.S. nonsmokers age 35 and over attributable to ETS (Chapter 6) is based on data pooled from all 11 U.S. epidemiologic studies of never-smoking women married to smoking spouses. Use of U.S. studies should increase the confidence in these estimates. Some mathematical modeling is required to adjust for expected bias from misclassification of smoking status and to account for ETS exposure from sources other than spousal smoking. Assumptions are also needed to relate responses in female never-smokers to those in male never-smokers and ex-smokers of both sexes, and to estimate the proportion of the nonsmoking population exposed to various levels of ETS. Overall, however, the assumptions necessary for estimating risk add far less uncertainty than other EPA quantitative assessments. This is because for ETS the extrapolation is based on a large database of human studies, all at levels actually expected to be encountered by much of the U.S. population.

The components of the 3,000 lung cancer deaths figure include approximately 1,500 female never-smokers, 500 male never-smokers, and 1,000 former smokers of both sexes. More females are estimated to be affected because there are more female than male nonsmokers. These component estimates have varying degrees of confidence; the estimate of 1,500 deaths for female never-smokers has the highest confidence because of the extensive database. The estimate of 500 for male never-smokers is less certain because it is based on the female never-smoker response and is thought to be low because males are generally subject to higher background ETS exposures than females. Adjustment for this higher background exposure would lead to higher risk estimates. The estimate of 1,000 lung cancer deaths for former smokers of both sexes is considered to have the lowest confidence, and the assumptions included are thought to make this estimate low as well.

Workplace ETS levels are generally comparable to home ETS levels, and studies using body cotinine measures as biomarkers demonstrate that nonhome exposures to ETS are often greater

2501031767

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

than exposure from spousal smoking. Thus, this report presents an alternative breakdown of the estimated 3,000 ETS-attributable lung cancer deaths between spousal and nonhome exposures. By extension of the results from spousal smoking studies, coupled with biological measurements of exposure, more lung cancer deaths are estimated to be attributable to ETS from combined nonhome exposures - 2,200 of both sexes - than from spousal exposure - 800 of both sexes. This home-versus-other-sources partitioning depends on current exposure estimates that may or may not be applicable to the exposure period of interest. Thus, this breakdown contains this element of uncertainty in addition to those discussed above with respect to the previous breakdown.

Other estimates of annual U.S. nonsmoker lung cancer deaths attributable to ETS developed in this document give a range of 2,500 to 3,300. These other estimates use both mortality and cotinine exposure data from the largest and best-designed U.S. study (Fontham et al., 1991). Relatively small differences in cotinine ratios, as measures of exposure from spousal smoking, can result in substantial variability in population risk estimates. The range suggested above provides an estimation of the uncertainty in these estimates. Overall, however, considering the multitude, consistency, and quality of all these studies, the weight-of-evidence conclusion that ETS is a known human lung carcinogen, and the limited amount of extrapolation necessary, the confidence in the estimate of approximately 3,000 lung cancer deaths is medium to high.

1.2.2. ETS and Noncancer Respiratory Disorders

Exposure to ETS from parental smoking has been previously linked with increased respiratory disorders in children, particularly in infants. Several studies have confirmed the exposure and uptake of ETS in children by assaying saliva, serum, or urine for cotinine. These cotinine concentrations were highly correlated with smoking (especially by the mother) in the child's presence. Nine million to twelve million American children under 5 years of age, or one-half to two-thirds of all children in this age group, may be exposed to cigarette smoke in the home (American Academy of Pediatrics, 1986).

With regard to the noncancer respiratory effects of passive smoking, this report focuses on epidemiologic evidence appearing since the two major reports of 1986 (NRC and U.S. DHHS) that bears on the potential association of parental smoking with detrimental respiratory effects in their children. These effects include symptoms of respiratory irritation (cough, sputum, or wheeze); acute diseases of the lower respiratory tract (pneumonia, bronchitis, and bronchiolitis); acute middle ear infections and indications of chronic middle ear infections (predominantly middle ear effusion); reduced lung function (from forced expiratory volume and flow-rate measurements);

250103176B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

incidence and prevalence of asthma and exacerbation of symptoms in asthmatics; and acute upper respiratory tract infections (colds and sore throats). The more than 50 recently published studies reviewed here essentially corroborate the previous conclusions of the NRC and Surgeon General regarding respiratory symptoms, respiratory illnesses, and pulmonary function, and they strengthen support for those conclusions by the additional weight-of-evidence (Chapter 7). For example, new data on middle ear effusion strengthen previous evidence to warrant the stronger conclusion in this report of a causal association with parental smoking. Furthermore, recent studies establish associations between parental smoking and increased incidence of childhood asthma. Additional research also supports the hypotheses that in utero exposure to mother's smoke and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization, changes that are known to predispose children to early respiratory illness. Early respiratory illness can lead to long-term pulmonary effects (reduced lung function and increased risk of chronic obstructive lung disease).

This document also summarizes the evidence for an association between parental smoking and SIDS, which was not addressed in the 1986 NRC or Surgeon General reports. SIDS is the most common cause of death in infants ages 1 month to 1 year. The cause (or causes) of SIDS is unknown; however, it is widely believed that some form of respiratory pathogenesis is generally involved. The current evidence strongly suggests that infants whose mothers smoke are at an increased risk of dying of SIDS, independent of other known risk factors for SIDS, including low birthweight and low gestational age, which are specifically associated with active smoking during pregnancy. However, available studies do not allow this report to conclude whether that increased risk is related to in utero versus postnatal exposure to tobacco smoke products, or to both.

The 1986 NRC and Surgeon General reports conclude that both the prevalence of respiratory symptoms of irritation and the incidence of lower respiratory tract infections are higher in children of smoking parents. In the 18 studies of respiratory symptoms subsequent to the 2 reports, increased symptoms (cough, phlegm, and wheezing) were observed in a range of ages from birth to midteens, particularly in infants and preschool children. In addition to the studies on symptoms of respiratory irritation, nine new studies have addressed the topic of parental smoking and acute lower respiratory tract illness in children, and eight have reported statistically significant associations. The cumulative evidence indicates strongly that parental smoking, especially the mother's, causes an increased incidence of respiratory illnesses from birth up to the first 18 months to 3 years of life, particularly for bronchitis, bronchiolitis, and

2501031769

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

pneumonia. Overall, the evidence confirms the previous conclusions of the NRC and Surgeon General.

Recent studies also solidify the evidence for the conclusion of a causal association between parental smoking and increased middle ear effusion in young children. Middle ear effusion is the most common reason for hospitalization of young children for an operation.

At the time of the Surgeon General's report on passive smoking (U.S. DHHS, 1986), data were sufficient only to conclude that maternal smoking may influence the severity of asthma in children. The recent studies reviewed here strengthen and confirm these exacerbation effects. In addition, the new evidence is conclusive that ETS exposure increases the number of episodes of asthma in children who already have the disease. It is also suggestive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms, although the results are statistically significant only with children whose mothers smoke 10 or more cigarettes per day. While the evidence for new cases of asthma itself is not conclusive of a causal association, the consistent strong associations of ETS with both increased frequency and severity of the asthmatic symptoms and the established ETS effects on both the immune system and airway hyperresponsiveness lead to the conclusion that ETS is a risk factor for induction of asthma in previously asymptomatic children.

Regarding the effects of passive smoking on lung function in children, the 1986 Surgeon General and NRC reports both conclude that children of parents who smoke have small decreases in tests of pulmonary output function of both the larger and smaller air passages when compared with the children of nonsmokers. As noted in the NRC report, if ETS exposure is the cause of the observed decrease in lung function, the effect could be due to the direct action of agents in ETS or an indirect consequence of increased occurrence of acute respiratory illness related to ETS.

Results from eight studies on ETS and lung function in children that have appeared since those reports add some additional confirmatory evidence suggesting a causal rather than an indirect relationship. For the population as a whole, the reductions are small relative to the interindividual variability of each lung function parameter. However, groups of particularly susceptible or heavily exposed subjects have shown larger decrements. The studies reviewed suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. Exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

2501031770

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

With respect to lung function effects in adults exposed to ETS, the 1986 NRC and Surgeon General reports found the data at that time inconclusive, due to high interindividual variability and the existence of a large number of other risk factors, but compatible with subtle deficits in lung function. Recent studies confirm the association of passive smoking with small reductions in lung function. Furthermore, new evidence also has emerged suggesting a subtle association between exposure to ETS and increased respiratory symptoms in adults.

There is some evidence suggesting that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

In reviewing the available evidence indicating an association (or lack thereof) between ETS exposure and the different noncancer respiratory disorders analyzed in this report, the possible role of several potential confounding factors was considered. These include other indoor air pollutants; socioeconomic status; effect of parental symptoms; and characteristics of the exposed child, such as low birthweight or active smoking. No single or combined confounding factors can explain the observed respiratory effects of passive smoking in children.

For diseases for which ETS has been either causally associated (lower respiratory tract infections) or indicated as a risk factor (asthma cases in previously asymptomatic children), estimates of population attributable risk can be calculated. A population risk assessment (Chapter 8) provides a probable range of estimates that 8,000 to 26,000 cases of childhood asthma per year are attributable to ETS exposure from mothers who smoke 10 or more cigarettes per day. The confidence in this range of estimates is medium and is dependent on the suggestive evidence of the database. While the data show an effect only for children of these heavily smoking mothers, additional cases due to lesser ETS exposure are also a possibility. If the effect of this lesser exposure is considered, the range of estimates of new cases presented above increases to 13,000 to 60,000. Furthermore, this report estimates that the additional public health impact of ETS on asthmatic children includes over 200,000 children whose symptoms are significantly aggravated and as many as 1,000,000 children who are affected to some degree.

This report estimates that ETS exposure contributes 150,000 to 300,000 cases annually of lower respiratory tract illness in infants and children younger than 18 months of age and that 7,500 to 15,000 of these will require hospitalization. The strong evidence linking ETS exposure to increased incidence of bronchitis, bronchiolitis, and pneumonia in young children gives these

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

estimates a high degree of confidence. There is also evidence suggesting a smaller ETS effect on children between ages 18 months and 3 years, but no additional estimates have been computed for this age group. Whether or not these illnesses result in death has not been addressed here.

In the United States, more than 5,000 infants die of SIDS annually. It is the major cause of death in infants between the ages of 1 month and 1 year and the linkage with maternal smoking is well established. The Surgeon General and World Health Organization estimate that more than 700 U.S. infant deaths per year from SIDS are attributable to maternal smoking (U.S. CDC, 1991a). However, this report concludes that at present there is not enough direct evidence supporting the contribution of ETS exposure to declare it a risk factor or to estimate its population impact on SIDS.

2501031772

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

2. INTRODUCTION

An estimated 434,000 deaths per year in the United States, or more than one of every six deaths, are directly attributable to tobacco use, in particular cigarette smoking (CDC, 1991a; figures for 1988). Approximately 112,000 of these smoking-related deaths are from lung cancer, accounting for an estimated 87% of U.S. lung cancer mortality (U.S. DHHS, 1989; percentage for 1985). Cigarette smoking is also causally related to cancer at various other sites, such as the bladder, renal pelvis, pancreas, and upper respiratory and digestive tracts (IARC, 1986). Roughly 30,000 deaths per year from cancers at these sites are attributable to smoking (CDC, 1991a). Furthermore, smoking is the major cause of chronic obstructive pulmonary disease (COPD), which includes emphysema, and is thought to be responsible for approximately 61,000 COPD deaths yearly, or about 82% of COPD deaths (U.S. DHHS, 1989). Tobacco use is also a major risk factor for cardiovascular diseases, the leading cause of death in the United States. It is estimated that each year 156,000 heart disease deaths and 26,000 deaths from stroke are attributable to smoking (CDC, 1991a). In addition to this substantial mortality, the association of smoking with these conditions also involves significant morbidity.

Smoking is also a risk factor for various respiratory infections, such as influenza, bronchitis, and pneumonia. An estimated 20,000 influenza and pneumonia deaths per year are attributable to smoking (CDC, 1991a). Smokers also suffer from lung function impairment and numerous other respiratory symptoms, such as cough, phlegm production, wheezing, and shortness of breath. In addition, smokers are at increased risk for a variety of other conditions, including pregnancy complications and ulcers.

Although the exact mechanisms and tobacco smoke components associated with these health effects are not known with certainty, more than 40 known or suspected human carcinogens have been identified in tobacco smoke. These include, for example, benzene, nickel, polonium-210, 2-napthylamine, 4-aminobiphenyl, formaldehyde, various N-nitrosamines, benz[a]anthracene, and benzo[a]pyrene. Many other toxic agents, such as carbon monoxide, nitrogen oxides, ammonia, and hydrogen cyanide, are also found in tobacco smoke.

Smokers, however, are not the only ones at risk from exposure to these tobacco smoke toxicants. In utero exposure from maternal smoking is known to be associated with low birthweight and increased risk of fetal and infant death (U.S. DHHS, 1989). Furthermore, nonsmokers might be at risk for smoking-associated health effects from passive exposure to environmental tobacco smoke (ETS). When a cigarette is smoked, approximately half of the

2501031773

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

smoke generated is sidestream smoke (SS) emitted from the smoldering cigarette between puffs. This SS constitutes roughly 85% of ETS (Fielding, 1985).

Twenty-eight percent of the U.S. adult population (CDC, 1991b), or about 50 million Americans, are smokers, and so virtually all Americans are exposed to some amount of ETS in the home, at work, or in public places. In view of the high levels of mortality and morbidity associated with smoking and the considerable potential for exposure of nonsmokers to ETS, passive smoking is potentially a substantial public health concern.

2.1. FINDINGS OF PREVIOUS REVIEWS

The first epidemiologic results associating passive smoking with lung cancer appeared in the early 1980's. Since then, two major comprehensive reviews of the health effects of passive smoking, and several less extensive ones have been published. One of the major reviews was conducted by the National Research Council (NRC) in 1986. At the request of two Federal agencies, the U.S. Environmental Protection Agency and the U.S. Department of Health and Human Services, the NRC formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on all of the potential health consequences of exposure. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail and includes summary analyses from 10 case-control studies and 3 cohort (prospective) studies. The report concludes that "[c]onsidering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers." Combining the data from all the studies, the committee calculated an overall observed relative risk estimate of 1.34 (95% C.I. = 1.18-1.53).

The NRC committee was concerned about potential bias in the study results caused by current and former smokers incorrectly self-reported as lifelong nonsmokers (never-smokers). Using plausible assumptions for misreported smoking habits, the committee determined that smoker misclassification cannot account for all of the increased risk observed in the epidemiologic studies. Furthermore, the upward bias on the relative risk of lung cancer caused by smoker misclassification is counterbalanced by the downward bias from background ETS exposure to the supposedly unexposed group. Correcting for smoker misclassification and background ETS exposure, the committee calculated an overall adjusted relative risk estimate of 1.42 (range of 1.24 to 1.61) for lung cancer in nonsmokers from exposure to ETS from spousal smoking plus background sources.

2501031724

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The NRC committee also found evidence for noncancer respiratory effects in children exposed to ETS. It recommended that "[i]n view of the weight of the scientific evidence that ETS exposure in children increases the frequency of pulmonary symptoms and respiratory infections, it is prudent to eliminate smoking and resultant ETS from the environments of small children." Furthermore, the committee concluded that "[h]ousehold exposure to ETS is linked with increased rates of chronic ear infections and middle ear effusions in young children." The NRC report also notes that "[e]vidence has accumulated indicating that nonsmoking pregnant women exposed to ETS on a daily basis for several hours are at increased risk for producing low-birthweight babies, through mechanisms which are, as yet, unknown."

The second major review, the Surgeon General's report on the health consequences of passive smoking, also appeared in 1986 (U.S. DHHS, 1986). This review covers ETS chemistry, exposure, and various health effects, primarily lung cancer and childhood respiratory disease. On the subject of lung cancer, the report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer.

With respect to respiratory disorders in children, the Surgeon General's report determined that "[t]he children of parents who smoke, compared with the children of nonsmoking parents, have an increased frequency of respiratory infections, increased respiratory symptoms, and slightly smaller rates of increase in lung function as the lung matures."

In 1987, a committee of the International Agency for Research on Cancer (IARC) issued a report on methods of analysis and exposure measurement related to passive smoking (IARC, 1987). The committee reviewed the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. The report borrows the summary statement on passive smoking from a previous IARC document that dealt mainly with tobacco smoking (IARC, 1986). The working group that produced the 1986 report had found that the epidemiologic evidence then available on passive smoking was compatible with either the presence or the absence of a lung cancer risk; however, based on other considerations related to biological plausibility, it concluded that passive smoking gives rise to some risk of cancer. Specifically, the 1986 IARC report states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive smoking," and of the quantitative relationships between

2501031775

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

> dose and effect that are commonly observed from exposure to carcinogens . . . leads to the conclusion that passive smoking gives rise to some risk of lung cancer.

More recently, the Working Group on Passive Smoking, an independent international panel of scientists supported in part by RJR Reynolds Nabisco, reported the findings of its comprehensive "best evidence synthesis" of over 2,900 articles on the health effects of passive smoking (Spitzer et al., 1990). The group concluded that "[t]he weight of evidence is compatible with a positive association between residential exposure to environmental tobacco smoke (primarily from spousal smoking) and the risk of lung cancer." It also found "strong evidence that children exposed in the home to environmental tobacco smoke have higher rates of hospitalization (50 to 100%) for severe respiratory illness" and that the "evidence strongly supports a relationship between exposure to environmental tobacco smoke and asthma among children." In addition, the working group reported that there is evidence for associations between home ETS exposure and many chronic and acute respiratory illnesses, as well as small decreases in physiologic measures of respiratory function, in both children and adults. Evidence demonstrating an increased prevalence of otitis media (inflammation of the middle ear) in children exposed to ETS at home was also noted. With respect to in utero exposure, the group concluded that active maternal smoking is associated with reduced birthweight and with increased infant mortality.

A recent review of the health effects associated with adult workplace exposure to ETS conducted by the National Institute for Occupational Safety and Health (NIOSH, 1991) determined that "the collective weight of evidence (i.e., that from the Surgeon General's reports, the similarities in composition of MS [mainstream smoke] and ETS, and the recent epidemiologic studies) is sufficient to conclude that ETS poses an increased risk of lung cancer and possibly heart disease to occupationally exposed workers." Furthermore:

> Although these data were not gathered in an occupational setting, ETS meets the criteria of the Occupational Safety and Health Administration (OSHA) for classification as a potential occupational carcinogen [Title 29 of the Code of Federal Regulations, Part 1990]. NIOSH therefore recommends that exposures be reduced to the lowest feasible concentration.

The classification of "potential occupational carcinogen" is NIOSH's category of strongest evidence for carcinogenicity.

2.2. EPA's 1992 DOCUMENT

2.2.1. Scope

Due to the serious health concerns that have arisen regarding ETS, the most ubiquitous indoor air pollutant, and the wealth of new information that has become available since the

250103177G

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

extensive 1986 reviews, the EPA has performed its own analytical hazard identification and risk assessment for the respiratory health effects of passive smoking, based on a critical review of the data currently available, with an emphasis on the abundant epidemiologic evidence. The number of lung cancer studies analyzed in this document is more than double the number reviewed in 1986 (31 vs. 13), with a total of about 3,000 lung cancer cases in female nonsmokers now reported in case-control studies and almost 300,000 female nonsmokers followed by cohort studies. Furthermore, the database on passive smoking and respiratory disorders in children contains more than 50 new studies, including 8 additional studies on acute lower respiratory tract illnesses, 9 on acute and chronic middle ear diseases, 18 on respiratory symptoms, 9 on asthma, and 8 on lung function. This report also discusses six recent studies of the effects of passive smoking on adult respiratory symptoms and lung function. Finally, eight studies of maternal smoking and sudden infant death syndrome (SIDS), which was not addressed in the NRC report or the Surgeon General's report, are reviewed. (Although the cause of SIDS is unknown, the most widely accepted hypotheses suggest that some form of respiratory pathogenesis is usually involved.)

First, this document reviews information on the nature of ETS and human exposures. Then, in accordance with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), it critically analyzes human, animal, and genotoxicity data to establish the weight-of-evidence for the hazard identification of ETS as a human lung carcinogen and to characterize the U.S. population risk. Similarly, it reviews studies of passive smoking and noncancer respiratory disorders, particularly in children, and provides both hazard identification and population risk estimates for some of these effects.

While this report restricts analysis to ETS-associated respiratory effects because of time and resource considerations, several recent studies have also linked passive smoking with an increased risk of heart disease or cancers at sites other than the lung. For cancers of other sites, the available evidence is quite limited (e.g., Hirayama, 1984; Sandler et al., 1985), but three recent analyses, examining over 15 epidemiologic studies and various supporting mechanistic studies, suggest that ETS is an important risk factor for heart disease, accounting for as many as 35,000 to 40,000 deaths annually (Wells, 1988; Glantz and Parmley, 1991; Steenland, 1992). This report takes no position on ETS and heart disease.

Other health effects of active smoking may also have passive smoking correlates of public health concern. Maternal smoking during pregnancy, for example, is known to affect fetal development. Studies on passive smoking during pregnancy are far fewer but have demonstrated an apparent association with low birthweight (e.g., Martin and Bracken, 1986). Furthermore,

250103177

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

passive exposure to tobacco smoke products both in utero and postnatally may result in other nonrespiratory developmental effects in children--for example, decrements in neurological development (Makin et al., 1991). Again, this document takes no position on these potential nonrespiratory effects.

2.2.2. Use of EPA's Guidelines

The lung cancer hazard identification and risk characterization for ETS are conducted in accordance with the EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a). In fact, tobacco smoke is a mixture of over 4,000 compounds and could be evaluated according to the *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b). Such a highly complex mixture, however, is not easily characterized with respect to chemical composition, levels of exposure, and toxicity of constituents. Furthermore, the effects and mechanisms of interactions among chemicals are insufficiently understood.

The *Guidelines for the Health Risk Assessment of Chemical Mixtures* acknowledges these inherent uncertainties and recommends various assessment approaches, depending on the nature and quality of the data. When adequate data are available on health effects and exposure for the actual mixture of concern, as is the case with both MS and ETS, the preferred approach, according to the mixtures guidelines, is to adopt the procedures used for single compounds described by the *Guidelines for Carcinogen Risk Assessment*, as is done here. The EPA has also used this strategy for assessments of diesel exhausts, PCBs, and unleaded gasoline. The compilation of health effects and exposure information for all the mixture components of interest is considered optional. In the case of tobacco smoke, compiling this information would be highly impractical due to the large number of components and the highly complex and changing nature of this mixture. It is also considered unnecessary, given the abundant epidemiologic data on ETS and lung cancer.

The *Guidelines for Carcinogen Risk Assessment* provide a general framework for the analysis of carcinogenic risk, while permitting "sufficient flexibility to accommodate new knowledge and new assessment methods as they emerge" (U.S. EPA, 1986a). According to the guidelines, a qualitative risk assessment, or hazard identification, is performed by evaluating all of the relevant data to determine if a compound has carcinogenic potential. Then, a dose-response assessment is made by using mathematical models to extrapolate from high experimental or occupational exposures, where risks are usually detected, to lower environmental exposure levels.

2501031778

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Finally, the dose-response assessment and an exposure assessment are integrated into a risk characterization, providing risk estimates for exposed populations.

The enormous database on active and passive smoking provides more than sufficient human evidence on which to base a hazard identification of ETS. The use of human evidence eliminates the uncertainty that normally arises when one has to base hazard identification on the results of high-dose animal experiments. Furthermore, the epidemiologic data on passive smoking provide direct evidence from environmental exposure levels, obviating the need for a dose-response extrapolation from high to low doses. These low-level environmental exposures, however, are associated with low relative risks that can only be detected in well-designed studies of sufficiently large size. For this reason, new assessment methods are used to categorize studies on the basis of quality criteria and to combine studies to increase the statistical power.

As an alternative to using actual epidemiologic data on ETS, an ETS risk assessment could have used "cigarette equivalents" to correlate ETS exposure with lung cancer risk based on dose-response models from active smoking. This would have involved using measures such as cotinine or respirable suspended particles to compare smoke uptake between smokers and ETS-exposed nonsmokers in order to equate passive smoking to the active smoking of some quantity of a cigarette(s). Then the carcinogenic response associated with that exposure level would be estimated from extrapolation models based on the dose-response relationships observed for active smoking. This procedure was not used for several reasons. Although MS and ETS are qualitatively similar with respect to chemical composition (i.e., they contain most, if not all, of the same toxicants and carcinogens), the absolute and proportional quantities of the components, as well as their physical state, can differ substantially. Many tobacco smoke compounds partition preferentially into the MS component of smoke emissions; others, however, such as certain highly carcinogenic N-nitrosamines, are preferentially produced at lower temperatures and appear in much greater amounts in the ETS fraction. In addition, active and passive smokers have different breathing patterns, and particles in ETS are smaller than those in MS. Therefore, the distribution and deposition of smoke constituents in the respiratory tracts of active and passive smokers will not be identical. Furthermore, it is not known which of the chemicals in tobacco smoke are responsible for its carcinogenicity. Clearly the comparison of a small number of biomarker measures cannot adequately quantify differential distributions of unknown carcinogenic compounds.

Another area of uncertainty in the "cigarette equivalents" approach relates to potential metabolic differences between active and passive smokers. Active smoking is known to induce

2501031779

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

chemical- and drug-metabolizing enzymes in various tissues to levels that significantly exceed those found in nonsmokers. Thus, the dose-response relationships for tobacco smoke-associated health effects are likely to be nonlinear. In fact, evidence suggests that a linear dose-response extrapolation might underestimate the risk of adverse health effects from low doses of tobacco smoke (Remmer, 1987). Because of these uncertainties, the data from active smoking are more appropriate for qualitative hazard identification than for quantitative dose-response assessment. Furthermore, at least for lung cancer and other respiratory effects, we have substantial epidemiologic data from actual exposure of nonsmokers to environmental levels of genuine ETS, which constitute a superior database from which to derive quantitative risk estimates for passive smoking, without the need for low-dose extrapolation.

2.2.3. Contents of This Document

ETS is chemically similar to MS, containing most, if not all, of the same toxicants and known or suspected human carcinogens. A major difference, however, is that ETS is rapidly diluted into the environment, and consequently, passive smokers are exposed to much lower concentrations of these agents than are active smokers. Therefore, in assessing potential health risks attributable to ETS, it is important to be able to measure ETS levels in the many environments where it is found and to quantify actual human ETS exposure. The physical and chemical nature of ETS and issues related to human exposure are discussed in Chapter 3. The use of marker compounds and various methods for assessing ambient ETS concentrations, as well as the use of biomarkers, questionnaires, and modeling techniques to determine human exposure, is described. Furthermore, measurements of ETS components in various indoor environments and of ETS constituents and their metabolites in adult and child nonsmokers are presented, providing evidence of actual nonsmoker exposure and uptake.

Chapter 4 reviews the major evidence that conclusively established that the tobacco smoke inhaled from active smoking is a human lung carcinogen. Unequivocal dose-response relationships exist between tobacco smoking and lung cancer, with no evidence of a threshold level of exposure. Supporting evidence for the carcinogenicity of tobacco smoke from animal bioassays and genotoxicity experiments is also summarized, including data from the limited animal and mutagenicity studies pertaining specifically to ETS.

The chemical similarity between MS and ETS and the measurable uptake of ETS constituents by nonsmokers (Chapter 3), as well as the causal dose-related association between tobacco smoking and lung cancer in humans, extending to the lowest observed doses, and the

250103178O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

corroborative evidence for the carcinogenicity of both MS and ETS provided by animal bioassays and genotoxicity studies (Chapter 4), clearly establish the biological plausibility that ETS is also a human lung carcinogen. In fact, this evidence is sufficient in its own right to establish weight-of-evidence for ETS as a Group A (known human) carcinogen under EPA guidelines.

In addition to the evidence of human carcinogenicity from high exposures to tobacco smoke from active smoking, there are now more than 30 epidemiologic studies investigating lung cancer in nonsmokers exposed to actual ambient levels of ETS. The majority of these studies examine never-smoking women, with spousal smoking used as a surrogate for ETS exposure. Female exposure from spousal smoking is considered to be the single surrogate measure that is the most stable and best represents ETS exposure.

For the purposes of the hazard identification analysis in Chapter 5, which is based primarily on the epidemiologic studies of ETS, this document extensively and critically evaluates 31 epidemiologic studies from 8 different countries, including 11 studies from the United States (Appendix A). More than half of these studies have appeared since the NRC and Surgeon General's reviews were issued in 1986. Two U.S. studies are of particular interest. The recently published five-center study of Fontham et al. (1991) is a well-designed and conducted case-control study with 429 never-smoking female lung cancer cases and two separate sets of controls. This is the largest case-control study to date, and it has a high statistical power to detect the small increases in lung cancer risk that might be expected from ambient exposures. Another large U.S. case-control study was the recent study by Janerich et al. (1990), with 191 cases. Both of these studies were supported by the National Cancer Institute.

In evaluating epidemiologic studies, potential sources of bias and confounding must also be addressed. Smoker misclassification of current and former smokers as never-smokers is the one identified source of systematic upward bias to the relative risk estimates. Therefore, prior to the statistical analyses of the epidemiologic data that are conducted in Chapter 5, the relative risk estimates from each study are adjusted for smoker misclassification using the methodology of Appendix B. Other potential sources of bias and confounding are discussed extensively in the course of Chapter 5.

Chapter 5 quantitatively and qualitatively analyzes the epidemiologic data to determine the weight-of-evidence for the hazard identification of ETS. First the individual studies are statistically assessed using tests for effect (i.e., association between lung cancer and ETS) and tests for dose-response trend. Then various combining analyses are performed to examine and compare the epidemiologic results for separate countries. The studies are also categorized into four tiers

250103178

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

according to the utility of the study in terms of its likely ability to detect a possible effect, based on specific criteria for evaluating the design and conduct as displayed in Appendix C and the critical reviews in Appendix A. These tiers are integrated one at a time into statistical analyses, as an alternative method for evaluating the epidemiologic data that also takes into account qualitative considerations. Chapter 5 concludes with an overall weight-of-evidence determination for lung cancer based on the analyses in Chapters 3, 4, and 5.

In Chapter 6, the relative risk estimates from 11 U.S. studies of passive smoking and lung cancer are adjusted upward to correct for the systematic downward bias caused by background exposure to ETS from sources other than spousal smoke. Using additional assumptions to extend the results from female never-smokers to male never-smokers and long-term former smokers of both sexes, the population risk for U.S. nonsmokers is characterized by estimating the annual number of lung cancer deaths that are attributable to exposure from all sources of ETS. Separate estimates are calculated for background (workplace and other nonhome exposures) and spousal (home) exposures, as well as for female and male never-smokers and former smokers. Chapter 6 also discusses the sources of uncertainty and sensitivity in the lung cancer estimates.

The final two chapters address passive smoking and noncancer respiratory disorders. Both the NRC and Surgeon General's reports concluded that children exposed to ETS from parental smoking are at greater risk for various respiratory illnesses and symptoms. This document confirms and extends those conclusions with analyses of more recent studies. New evidence for an association between ETS and middle ear effusion, and for a role of ETS in the cause as well as in the prevalence and severity of childhood asthma, is reviewed. In addition, the evidence for an association between maternal smoking and SIDS is examined.

Chapter 7 reviews and analyzes epidemiologic studies of passive smoking and noncancer respiratory disorders, mainly in children. Possible biological mechanisms, additional risk factors, and the potential long-term significance of early effects on lung function are discussed. Then, the evidence indicating relationships between childhood exposure to ETS and acute respiratory illnesses, middle ear disease, chronic respiratory symptoms, asthma, and lung function impairment, and between maternal smoking and SIDS, is evaluated.

Passive smoking as a risk factor for noncancer respiratory health effects in adults is also analyzed in Chapter 7. The NRC and Surgeon General's reports concluded that adults exposed to ETS may exhibit small deficits in lung function but noted that it is difficult to determine the extent to which ETS impairs respiration because so many other factors can similarly affect lung

2501031782

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

function. More recent evidence and new statistical techniques allow the demonstration of subtle effects of ETS on lung function and respiratory health in adults.

Chapter 8 discusses potential confounding factors and possible sources of bias in the ETS studies that might affect the conclusions of Chapter 7. Chapter 8 also describes methodological and data considerations that limit quantitative estimation of noncancer respiratory health effects attributable to ETS exposure. Finally, the chapter develops population impact assessments for ETS-attributable childhood asthma and for infant/toddler bronchitis and pneumonia. Acute respiratory illnesses are one of the leading causes of morbidity and mortality during infancy and early childhood, and an estimated 2 to 5 million children under age 18 are afflicted with asthma. Therefore, even small increases in individual risk for these illnesses can result in a substantial public health impact.

25010317 83

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

3. ESTIMATION OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE

3.1. INTRODUCTION

This chapter considers some of the major issues relevant to assessing human exposure to environmental tobacco smoke (ETS). Current information on the nature of ETS, use of marker or proxy compounds for ETS, measured personal exposures to ETS proxies, measured concentrations of ETS proxy air contaminants in various indoor environments, use of ETS biomarkers, current models for assessing ETS proxy concentrations, and use of questionnaires for assessing exposure to ETS is summarized and discussed.

In the course of a typical day, an individual spends varying amounts of time in a variety of microenvironments (e.g., residences, industrial and nonindustrial workplaces, automobiles, public access buildings, outdoors). While in these microenvironments, individuals are exposed to a broad and complex spectrum of organic and inorganic chemicals in gaseous and particle forms, as well as a range of viable particles.

ETS is a major source of indoor air contaminants because of the large, though decreasing, number of smokers in the population and the quantity and quality of the contaminants emitted into the environment from tobacco combustion (NRC, 1981, 1986). Although no national surveys have been published, the ubiquitous nature of ETS in indoor environments indicates that some unintentional inhalation of ETS by nonsmokers is unavoidable. The combustion of tobacco results in the emission of a particularly complex array of air contaminants into indoor microenvironments. The nature of the resultant ETS contaminant mix and eventual human exposure is the product of the interaction of several interrelated factors associated with the source, transport, chemical transformation, dispersal, and removal, as well as human activities. Efforts to determine adverse health and nuisance effects of ETS must address the issue of exposure to a complex mixture that occurs in a number of microenvironments and must recognize that assessing ETS exposures is inherently complicated. Fully assessing ETS exposures would involve determining the time-weighted sum of exposures to each constituent in a multiplicity of microenvironments. Because this cannot be done, a simplified approach using biological or atmospheric markers, or questionnaires is generally used.

Accurate methods of assessing ETS exposures are needed for conducting epidemiologic studies, for calculating risks, and for developing effective control measures to reduce or eliminate risks. In epidemiologic studies of ETS, accurate exposure information is crucial to minimize the effects of misclassification and the influence of confounders and to improve the probability of

2501031784

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

revealing exposure-response associations. In risk assessment, exposure assessment provides basic information on the exposure-distribution curve (populations at a range of exposures) for ETS and essential information to calculate dose. ETS exposure assessment is essential in developing cost-effective mitigation efforts to reduce or minimize ETS-associated risks and then to monitor progress toward the targeted risk reduction.

Effective exposure assessment efforts require the identification of the health or nuisance effect under study, the specification (when possible) of the biological response time of the effect, and the ascertainment of the individual air contaminant, general group of air contaminants, or contaminant source thought to be associated with that effect. It is difficult to identify a single effect associated with a single air contaminant exposure and even more difficult to determine a dose-response relationship. The outcome variable under study is generally part of an effect complex related to other risk variables (e.g., health status, age, race, diet, personal habits, occupation) and a variety of air contaminants emitted from a number of potential sources. It is important to specify the duration, frequency, and magnitude of exposure to specific contaminants or categories of contaminants on a time scale corresponding to the health or comfort effect. Such a specification is necessary if an appropriate and adequate exposure assessment effort is to be undertaken. For example, studies of ETS-associated chronic effects (e.g., cancer) would ideally have ETS exposure measures integrated over periods of years, whereas studies of ETS-associated acute effects (e.g., odor, eye irritation) require exposure measures over a period of a few minutes. Specification of the biological response time under study is important in developing an ETS exposure assessment strategy.

Exposure to individual air contaminants, categories of air contaminants, or sources of air contaminants found outdoors and indoors can be assessed by direct and indirect methods. Direct methods include personal monitoring and use of biological markers, measured in the subject population. The indirect method employs models to estimate exposures. The modeling approach can employ the use of stationary monitoring and questionnaires. Stationary monitoring, with passive or active methods, is used to measure concentrations of air contaminants in different environments. These measured concentrations are then combined with time activity patterns (time budgets) to determine the average exposure of an individual as the sum of the concentrations in each environment weighed by the time spent in that environment. Monitoring of contaminants might also be supplemented with the monitoring of factors in the environment that impact the contaminant levels measured (e.g., meteorological variables, primary compounds, ventilation). Measurement of these factors in a carefully chosen set of conditions can lead to models that

250103178S

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

predict concentrations in the absence of measured concentrations and provide a means of assessing the impact of efforts to reduce or eliminate exposures. Questionnaires are used to determine time activity patterns of individuals, to provide a simple categorization of potential exposure, and to obtain information on the properties of the environment that have an impact on the measured levels (e.g., presence of sources, source use).

3.2. PHYSICAL AND CHEMICAL PROPERTIES

ETS comprises aged exhaled mainstream smoke (MS) from the smoker, diluted sidestream smoke (SS) emitted from the smoldering tobacco between puffs, contaminants emitted into the air during the puff, and contaminants that diffuse through the cigarette paper (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992). SS is the principal contributor to ETS.

Chemical characterization of MS and SS air contaminant emissions from cigarettes, cigars, or pipes is derived from laboratory-based studies that have typically used standardized testing protocols (Brunnemann et al., 1976; Wynder and Hoffman, 1967; Dube et al., 1982). The data available are primarily for tobacco combustion in cigarettes. These protocols employ smoking machines, set puff volumes and frequencies, and standardize air contaminant collection protocols (e.g., small chambers, Cambridge filters, chamber airflow rates). Existing protocols reflect conditions representative of human smoking practices of more than 30 years ago and do not reflect current human smoking parameters (NRC, 1986; U.S. DHHS, 1986). MS and SS air contaminant emission rates determined in these studies can be affected by a number of factors, such as puff volume, air dilution rate, paper porosity, and moisture content of the tobacco. Variability in any of the factors can affect the nature and quantity of the emissions.

Results of laboratory evaluations have indicated substantial similarities and some differences between MS and SS emissions from cigarettes (NRC, 1986; U.S. DHHS, 1986). The air contaminants emitted in MS and SS are very similar in their chemical composition. Differences in SS and MS emissions are attributable to differences in the temperature of combustion of the tobacco, pH, and degree of dilution with air, which is accompanied by a corresponding rapid decrease in temperature. SS is generated at a lower temperature (600°C vs. 900°C) and at a higher pH (6.7-7.5 vs. 6.0-6.7) than is MS. SS is diluted rapidly with air. The size of SS particles is smaller than MS particles (SS particle size is 0.01-1.0 μm, whereas MS particle size is 0.1-1.0 μm). At the higher pH of SS, the proportion of unprotonated nicotine in the smoke increases, with SS nicotine predominantly in the vapor phase, while, in MS, nicotine is principally particle phase.

25010317786

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

More than 4,000 compounds have been identified in laboratory-based studies of tobacco smoke (Dube et al., 1982). Part of the data available from these studies is shown in Table 3-1. It is immediately obvious from Table 3-1 that SS and MS contain many of the same notable air contaminants, including several known or suspected human toxic and carcinogenic agents (e.g., carbon monoxide, ammonia, nicotine, tobacco-specific nitrosamines, benzo[a]pyrene, benzene, cadmium, nickel, aromatic amines). More than 20 carcinogens have been identified in ETS. Many of these toxic and carcinogenic compounds are emitted at levels higher in SS than in MS. For example, *N*-Nitrosodimethylamine, a potent animal carcinogen, is emitted in quantities 20 to 100 times higher in SS than in MS. A number of recent studies indicate that although filtering MS (filter cigarettes) will reduce the MS emissions for a number of compounds, it does not substantially reduce the emission rates for most SS constituents, particularly for known toxic and carcinogenic compounds (Adams et al., 1987; Guerin et al., 1987; Higgins, 1987).

The available data indicate that tobacco combustion will result in the emission of known toxic and carcinogenic contaminants into the environment, resulting in exposure to these contaminants by nonsmokers. It is important to note, however, that although the SS emissions are higher than MS emissions for many compounds, the dilution rate into the environment of SS is rapid, thus substantially lowering actual exposure concentrations of the contaminants. In cases where the SS emissions or exhaled MS emissions are in direct proximity to a nonsmoker (e.g., an infant held by a smoking mother or father), the nonsmoker's exposure to ETS contaminants will be high.

Few emission data have been collected under conditions more typical of actual smoking conditions (e.g., using smokers rather than smoking machines). It is not known how the MS and SS air contaminant emission data for specific compounds generated by the standardized testing protocols compare to data gathered under conditions more representative of actual smoking.

3.3. ASSESSING ETS EXPOSURE

3.3.1. Markers for Environmental Tobacco Smoke

Although ETS is a major source of indoor air contaminants, the actual contribution of ETS to indoor air is difficult to assess in the background of many contaminants contributed from a variety of other indoor and outdoor sources. Relatively few of the thousands of individual constituents of the ETS mix have been identified and characterized. In addition, little is known about the role of individual ETS constituents in eliciting the adverse health and nuisance effects observed. However, the issue is not how to fully characterize the exposure to each ETS-related

250103178?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

contaminant, but rather how to obtain accurate quantitative measures of exposure to the entire ETS mixture. The measurement of all components in ETS is not feasible, practical, or even desirable because of limitations in knowledge of the mixture components related to the effects of interest as well as the feasibility and cost of sampling. It is necessary then to identify a marker (also referred to as a tracer, proxy, indicator, or surrogate) for ETS that, when measured, will accurately represent the frequency, duration, and magnitude of exposure to ETS. These markers can be chemicals measured in the air, biomarkers, models, or simple questionnaires.

There are important issues related to the measurement of a given marker compound to represent exposure to ETS. Ideally, an air contaminant marker for ETS should (1) vary with source strength, (2) be unique to the source, (3) be easily detected in air at low concentrations, (4) be similar in emission rates for a variety of tobacco products, (5) occur in a consistent ratio in air to other ETS components in the complex mix, and (6) be easily, accurately, and cost-effectively measured (Leaderer, 1990). The marker can be a specific compound (e.g., nicotine) or much less specific (e.g., respirable suspended particle mass). These criteria for selecting a suitable marker compound are the ideal criteria. In practice, no single contaminant or class of contaminants has been identified that would meet all the criteria. Selection of a suitable marker for ETS is reduced to satisfying as many of the criteria for judging a marker as is practical. In using a marker, it is important to state clearly the role of the marker and to note its limitations.

A number of marker or proxy compounds have been used to represent ETS concentrations in both field and chamber studies. Nicotine, carbon monoxide, 3-ethenylpyridine, nitrogen dioxide, pyridine, aldehydes, nitrous acid, acrolein, benzene, toluene, myosmine, and several other compounds have been used or suggested for use as markers or proxies for the vapor phase constituents of ETS (NRC, 1981, 1986; U.S. DHHS, 1986; Hammond et al., 1987; Eatough et al., 1986; Löfroth et al., 1989; Leaderer and Hammond, 1991). Tobacco-specific nitrosamines, particle phase nicotine and cotinine, solanesol, polonium-210, benzo[a]pyrene, potassium, chromium, and respirable suspended particle (RSP) mass (RSP mass $\leq 2.5\ \mu m$) are among the air contaminants used or suggested for use as markers for particle phase constituents of ETS (NRC, 1981, 1986; U.S. DHHS, 1986; Leaderer and Hammond, 1991; Benner et al., 1989; Hammond et al., 1988; Rickert, 1984). All the markers employed to date have some problems associated with their use. For example, carbon monoxide, nitrogen oxides, benzene, and RSP have many indoor and outdoor sources other than the combustion of tobacco, while other compounds, such as nitrosamines and benzo[a]pyrene, are sufficiently difficult to measure (e.g., concentrations in

2501031788

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

smoking environments are low and the cost of collection and analysis of samples is high) that their use is very limited.

At the present time, vapor phase nicotine and respirable suspended particulate matter are widely and most commonly used as markers of the presence and concentration of ETS for a variety of reasons associated with their ease of measurement, existing knowledge on the their emission rates from tobacco combustion, and their relationship to other ETS contaminants.

Vapor phase nicotine, the dominant form of nicotine in ETS (NRC, 1986; U.S. DHHS, 1986; Hammond et al., 1987; Eatough et al., 1986; Eudy et al., 1985), accounts for approximately 95% of the nicotine in ETS and is a good marker air contaminant for ETS. It is specific to tobacco combustion and emitted in large quantities in ETS (NRC, 1981, 1986; U.S. DHHS, 1986; Rickert et al., 1984; Eatough et al., 1990). Chamber measurements have shown that nicotine concentrations vary with source strength (Hammond et al., 1987; Hammond and Leaderer, 1987) and show little variability among brands of cigarettes despite variations in MS emissions (Leaderer and Hammond, 1991; Rickert et al., 1984). Field studies have shown that weekly nicotine concentrations are highly correlated with the number of cigarettes smoked (Leaderer and Hammond, 1991; Hammond et al., 1987; Mumford et al., 1989; Hammond et al., 1989). One large field study (Leaderer and Hammond, 1991) showed that weekly nicotine concentrations were strongly correlated with measured RSP levels as well as with reported number of cigarettes smoked. In this study, the slope of the regression line was 10.8, similar to the RSP/nicotine level seen in chamber studies. The RSP intercept was equal to background levels in homes without smoking. A comparable study by Miesner et al. (1989) of particulate matter and nicotine in workplaces found a similar ratio between RSP and nicotine. The utility of nicotine as an ETS marker is enhanced by the fact that recent advances in air sampling have resulted in the development of a variety of validated and inexpensive passive and active monitoring methods for measuring nicotine in indoor air environments and for personal monitoring (Hammond et al., 1987; Hammond and Leaderer, 1987; Marbury et al., 1990; Eatough et al., 1989a; Koutrakis et al., 1989; U.S. DHEW, 1977; Muramatsu et al., 1984; Oldaker and Conrad, 1987). In addition, measurements of nicotine and cotinine, a metabolite of nicotine, in blood, urine, and saliva are used extensively as biomarkers of exposure to ETS.

The combustion of tobacco results in substantial emissions of RSP. One small chamber study using a smoking machine found the average particle emission rate for 15 Canadian cigarettes to be 24.1 mg per cigarette with a range of 15.8 to 36.0 mg per cigarette (Rickert et al., 1984). A large chamber study using smokers reported an average particle emission rate of 17.1 mg for 12

2501031789

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

brands of American cigarettes (Leaderer and Hammond, 1991). This study noted that emission rates among brands are similar. Included in the RSP are a number of compounds of direct health concern--for example, many of the polycyclic aromatic hydrocarbons (NRC, 1986; U.S. DHHS, 1986; Table 3-1). There are a number of accepted methods to measure personal RSP exposures and concentrations in indoor environments (Ogden et al., 1989).

Studies of personal exposures to RSP and of RSP levels in indoor environments have shown elevated levels of RSP when any ETS exposure was reported (NRC, 1986; U.S. DHHS, 1986; Leaderer and Hammond, 1991; Repace and Lowrey, 1980; Ishizu, 1980). One study found a strong correlation between weekly residential RSP levels and reported number of cigarettes smoked (Leaderer and Hammond, 1991). At low smoking and high ventilation rates, however, it may be difficult to separate the ETS-associated RSP in a background of RSP from other indoor sources (e.g., kerosene heaters) or even from outdoor sources. Efforts to model ETS exposures for the purpose of assessing risks and the impact of various mitigation measures have often focused on predicting ETS-associated RSP concentrations (e.g., Leaderer, 1988; Repace and Lowrey, 1980).

3.3.2. Measured Exposures to ETS-Associated Nicotine and RSP

3.3.2.1. *Personal Monitors*

Personal monitoring allows for a direct integrated measure of an individual's exposure. Personal air monitoring employs samplers (worn by individuals) that record the integrated concentration of a contaminant that individuals are exposed to in the course of their normal activity for time periods of several hours to several days. The monitors can be active (employing pumps to collect and concentrate the air contaminant) or passive (working on the principle of diffusion). As with biomarkers, personal monitoring provides an integrated measure of exposure to air contaminants across a number of environments in which an individual spends time, but it does not provide direct information on concentrations of the air contaminant of interest in individual environments or on the level of exposure in each environment unless samples are taken in only one environment or are changed with each change of environment. Supplemental information (e.g., air monitoring of spaces, time-activity patterns) is needed to determine the contribution of each microenvironment to total exposure.

There are relatively few studies reported that have measured personal exposures to ETS-associated nicotine and RSP for nonsmoking individuals. The few reported studies for personal exposure to nicotine are summarized in Table 3-2. Personal exposures associated with specific indoor environments are presented. The indoor environments include the nonindustrial

250103179D

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

workplace, homes, restaurants, public buildings, and transportation-related indoor spaces. Table 3-2 also highlights the wide range of indoor environments in which ETS exposures take place and the wide range of personal exposures encountered in those environments. It is important to note, however, that there are relatively few observations available and that the observations for non-workplace nicotine exposures is dominated by the Japanese data (Muramatsu et al., 1984), which may not be representative of personal exposures in the United States. Because the data are limited, specific conclusions related to the contribution of different indoor environments to personal nicotine exposures associated with passive smoke cannot be drawn. The data do indicate, however, that a wide range of exposures to ETS occur in a variety of indoor environments where smoking is permitted. The data also indicate that the occupational and residential environments are important sources of exposure to ETS because of the levels encountered, which are comparable, and the length of time individuals spend in them.

Those studies of personal exposure to RSP for nonsmoking individuals that have attempted to stratify the collected data by ETS exposure are shown in Table 3-3. Three of the five studies represent exposures integrated over several microenvironments (e.g., residential, public buildings, occupational), while two studies report exposures for the workplace only. Individuals reporting exposure to ETS have substantially higher integrated exposures to RSP than do those reporting no exposure. Passive smoke exposure resulted in increases in personal RSP exposures beginning at 18 to 64 $\mu g/m^3$. It is difficult to assess the ETS contribution to personal RSP levels for each indoor environment for the 24-hour RSP personal exposures. The contribution of each of these indoor environments must be substantially higher than the 24-hour averages presented, because exposures presumably did not take place during sleeping hours or in all microenvironments. Table 3-3 demonstrates that the contribution of ETS-related RSP in the work environment to personal exposure is important and variable.

The most extensive study of personal exposures to RSP clearly demonstrates the impact on RSP levels from exposure to ETS (Spengler et al., 1985). In this study, outdoor, indoor, and personal 24-hour concentrations of RSP (particle diameter ≤ 3.5 μm) were obtained for a nonsmoking sample of 101 individuals. Of the 101, 28 persons reported some exposure to ETS in either the home or workplace, while 73 reported no ETS exposure. The cumulative frequency distributions of RSP for the ETS-exposed and non-ETS-exposed individuals and measured outdoor levels are shown in Figure 3-1. Those reporting ETS exposure had mean personal RSP levels 28 $\mu g/m^3$ higher than those reporting no ETS exposure (Table 3-3). A larger variation in RSP concentrations was also seen for those reporting ETS exposure.

25010317 91

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

3.3.2.2. *Measurements Using Stationary Monitors*

Concentrations of nicotine, RSP, and other ETS constituents in an enclosed space can exhibit a pronounced spatial and temporal distribution. The concentration is the result of a complex interaction of several important variables, including (1) the generation rate of the contaminants from the tobacco, (2) location in the space that smoking occurs, (3) the rate of tobacco consumption, (4) the ventilation or infiltration rate, (5) the concentration of the contaminants in the ventilation or infiltration air, (6) air mixing in the space, (7) removal of contaminants by surfaces or chemical reactions, (8) reemission of contaminants by surfaces, and (9) the effectiveness of any air cleaners that may be present. The choice of location for obtaining an RSP or nicotine measurement, the timing of sample collection, and the duration of sampling should take into consideration the aforementioned factors.

In the past several years, numerous studies have been conducted in a variety of indoor environments to determine the impact of tobacco combustion on levels of nicotine and RSP. These studies have employed a variety of protocols that used a diversity of air sampling techniques (e.g., passive, active, continuous integrative), sampled over highly varying timeframes (from minutes to several days), and collected highly variable information on factors affecting the measured concentrations (e.g., number of cigarettes smoked, volume of building, ventilation rates). In an attempt to present an overall view of the contribution of ETS to indoor air quality, only the summary results of the measured concentrations of ETS-associated nicotine and RSP will be discussed here. Several reviews of the studies evaluating the impact of ETS on indoor RSP levels have been conducted over the past few years, and a number of recent reports have discussed measured indoor levels of nicotine (e.g., NRC, 1986; U.S. DHHS, 1986; Leaderer and Hammond, 1991). More detailed information is provided in those reports and the individual study reports.

A summary of measured nicotine concentrations in various indoor environments where smoking was noted is summarized in Figure 3-2. The mean concentration, standard deviation, and maximum and minimum nicotine values recorded are presented. Also given in Figure 3-2 is the number of locations in which the measurements were taken and the reference in which the data were reported. Elevated nicotine levels were measured in all microenvironments in which smoking was reported. Measured nicotine levels, as would be expected, were highly variable, covering several orders of magnitude.

The home and workplace environments may represent the most important environments for exposure to ETS because of the length of time individuals spend there. For the four studies reported, nicotine levels in homes where smoking occurs ranged from less than 1 $\mu g/m^3$ (Leaderer

2501031792

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

and Hammond, 1991) to more than 14 $\mu g/m^3$ (U.S. DHEW, 1977). For two of the studies (Leaderer and Hammond, 1991; U.S. DHEW, 1977), nicotine concentrations represent weekly averages. Actual concentrations in the homes during nonsleeping occupancy (i.e., while smoking would be occurring) would be considerably higher than the levels presented in Figure 3-2 (a factor of 3 or higher). Workplace nicotine also demonstrated a wide range of concentrations, from near zero to more than 33 $\mu g/m^3$. In other environments, nicotine concentrations demonstrated considerable variability. It is important to note that short-term concentrations (on the order of minutes) are likely to show considerably more variability, resulting in considerably higher short-term peak exposures.

In one large study of residential levels of ETS-associated nicotine and RSP (Leaderer and Hammond, 1991), both were found to be highly correlated with reported number of cigarettes smoked. This study found that, consistent with chamber data, measured nicotine concentrations predicted the contribution to residential RSP levels from tobacco combustion (Figure 3-3). The data in Figure 3-3 might be used to estimate the RSP levels associated with tobacco combustion from the nicotine levels shown in Figure 3-2.

A substantial number of studies examining the impact of tobacco combustion on concentrations of RSP in various indoor environments have been reported. Many of these studies have reported outdoor RSP concentrations and indoor RSP levels without smoking as well as concentrations when smoking occurs. These studies are summarized in Figure 3-4. The sampling time for the presented data ranged from 1 minute to more than several days. A major portion of the data is for the residential indoor environment. Where smoking is reported, RSP levels are considerably higher than where it is not. RSP levels associated with smoking, like those for nicotine, demonstrated considerable variability ranging from a few $\mu g/m^3$ to more than 1 mg/m^3. Workplace RSP levels associated with smoking occupancy are comparable to residential RSP levels.

Indoor levels of nicotine and RSP associated with the combustion of tobacco are a function of several factors related to the generation, dispersal, and removal of ETS in enclosed environments. Thus, measured levels of these air contaminants indicate a wide range of concentrations. Figures 3-5 and 3-6 present a summary of the range of nicotine and ETS-associated particle concentrations measured by type of environment. The figures present the range of average values reported for each study and the minimum and maximum values reported. Only studies reporting sampling times over 4 hours were included in the residential and office summaries in Figures 3-5 and 3-6 because averaging time is more likely to represent the exposures associated with occupancy time (this included most of the studies for residential spaces shown in

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Figures 3-2 and 3-4). Because occupancy time in other environments (e.g., restaurants) is likely to be much shorter (for patrons, but not for service personnel), averaging times on the order of minutes or greater were considered for the other indoor environments presented in the figures. Indoor particulate levels associated with smoking occupancy (Figure 3-6) were calculated by subtracting particle levels for nonsmoking occupancy (presented in the studies) from the smoking occupancy levels. Thus, the increase in particle mass concentrations associated with ETS is presented in Figure 3-6.

The summary nicotine data (Figure 3-5) suggest that average nicotine values in residences with smoking occupancy will range from 2 $\mu g/m^3$ to approximately 10 $\mu g/m^3$, with high values up to 14 $\mu g/m^3$ and low values down to 0.1 $\mu g/m^3$. Average nicotine concentrations in offices with smoking occupancy show a range of average concentrations similar to that of residences, but with considerably higher maximum values. The data from other indoor spaces suggest considerable variability, particularly in the range of maximum values. The cumulative distribution of weekly nicotine measured in one study (Leaderer and Hammond, 1991) of a sample of 96 homes, with the levels for smoking occupancy emphasized, is shown in Figure 3-7.

Residential particle mass concentrations will increase from 18 to 95 $\mu g/m^3$ with smoking occupancy, while the recorded increases can be as high as 560 $\mu g/m^3$ or as low as 5 $\mu g/m^3$ (Figure 3-6). Figure 3-8 (Leaderer and Hammond, 1991) highlights the distribution of weekly RSP concentrations for residences with smoking occupancy. In that study, smoking residences had RSP concentrations approximately 29 $\mu g/m^3$ higher than nonsmoking homes. Average concentrations in offices with smoking occupancy will be lower on average than in residences. Restaurants, transportation, and other indoor spaces with smoking occupancy will result in a considerably wider range of average, minimum, and maximum increases in particle concentrations than in the residential or office environments.

As noted earlier, indoor air contaminant concentrations are the result of the interaction of a number of factors related to the generation, dispersal, and elimination of the contaminants. Source use is no doubt the most important factor. Few studies have measured contaminant concentrations as a function of the smoking rate in residences or offices, but some data are available. One study estimated an average weekly contribution to residential RSP of 2 to 5 $\mu g/m^3$ per cigarette (Leaderer et al., 1990), while another study estimated that a pack-a-day smoker would add 20 $\mu g/m^3$ to residential levels (Coghlin et al., 1989). Variations in residential RSP levels as a function of the number of smokers and over a period of several months are demonstrated in Figure 3-9 (Spengler et al., 1981). An association between the reported number

250103179h

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

of cigarettes and weekly residential nicotine and RSP levels for a sample of 96 homes (Leaderer and Hammond, 1991) is shown in Figure 3-10. Smoking clearly increases indoor concentrations of both nicotine and particle mass. Residential levels of both nicotine and particle mass increase with increasing levels of smoking. Because nicotine and particle mass are proxies for the complex ETS contaminant mix, it is expected that other ETS air contaminants, including the toxic and carcinogenic contaminants, will be elevated with smoking occupancy.

Children have been identified as a particularly sensitive group at health risk from exposure to ETS in the residential indoor environment (NRC, 1986; U.S. DHHS, 1986). One study has measured smoking status of the parents and weekly nicotine concentrations in the activity room and bedroom of 48 children under the age of 2 years. The results, shown in Table 3-4, indicate that activity room and bedroom concentrations of nicotine in the children's homes increase with the reported number of cigarettes smoked in the home by parents. Concentrations also increased with the number of reported smokers in the household. Correlation coefficients of more than 0.7 were calculated between nicotine concentrations and number of cigarettes smoked.

It is important to note that while measurements of nicotine and ETS-associated RSP are excellent indicators of the contribution of ETS to air contaminant levels in indoor environments, their measurement does not directly constitute a measure of total exposure. The concentrations measured in all indoor environments have to be combined with time-activity patterns in order to determine average exposure of an individual as the sum of the concentrations in each environment weighted by the time spent in that environment. Both the home and the work environment (those without policies restricting smoking) have highly variable ETS concentrations, the ranges of which are largely overlapping. Which environment is most important in determining total exposure will vary with individual circumstances. For example, one who lives in a smoker-free home but works in an office with smokers will receive most ETS exposure at work; however, for those exposed both at home and at work, the home may be more important because, over the course of a week, more time is spent at home (assuming equal exposure concentrations).

An additional issue to be considered is how well the general indoor concentrations represent exposures of individuals who may be directly exposed to the SS plume of ETS. Small children, particularly infants, being held by smoking parents may receive exposures considerably higher than those predicted from concentrations reported for indoor spaces. Special consideration must be given to these significant subpopulations.

2501031795

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

3.3.3. Biomarkers of ETS Exposure

Biomarkers of exposure are actually a measure of dose or uptake and hence an indicator that an exposure has taken place. Biomarkers, within the context of assessing exposure to air contaminants, refer to cellular, biochemical, or molecular measures that are obtained from biological media such as human tissues, cells, or fluids and are indicative of human exposure to air contaminants (Collier et al., 1990; Goldstein et al., 1987). The relation between the biomarker and exposure, however, is complex and varies as a function of several factors, including environmental factors and the uptake, distribution, metabolism, and site and mode of action of the compound or compounds of interest.

Ideally, a biomarker of exposure for a specific air contaminant should be chemically specific, have a long half-life in the body, be detectable in trace quantities with high precision, be measurable in samples easily collected by noninvasive techniques, be inexpensive to assay, be either the agent that is associated with the effects or strongly associated with the agent of interest, and be quantitatively relatable to a previous exposure regimen. Ideal biomarkers for air contaminants, such as markers for complex mixtures, do not exist.

Numerous biomarkers have been proposed as indicators for ETS (e.g., thiocyanate, carboxyhemoglobin, nicotine and cotinine, N-Nitrosoproline, aromatic amines, protein or DNA adducts) (NRC, 1986; U.S. DHHS, 1986). Although these biomarkers demonstrate that an exposure has taken place, they may not be directly related to potential for development of the adverse effect under study (not the contaminant directly implicated in the effect of interest), they can show considerable variability from individual to individual, and they represent only fairly recent exposure (potentially inadequate for chronic outcomes). Furthermore, some of these markers may not be specific to ETS exposure (e.g., carboxyhemoglobin), while others (e.g., thiocyanate) may not be sensitive enough for ETS exposures.

Nicotine and its metabolite, cotinine, in the saliva, blood, and urine are widely used as biomarkers of active smoking and exposure to ETS and are valuable in determining total or integrated short-term dose to ETS across all environments (NRC, 1986; U.S. DHHS, 1986). Nicotine and cotinine are specific to tobacco and are accurately measured by gas chromatography, radioimmunoassay, or high-pressure liquid chromatography in concentrations down to 1 ng/ml. Nicotine has a half-life typically of about 2 hours in the blood and is metabolized to cotinine and excreted in the urine. The short half-life of nicotine makes it a better indicator of very recent exposures rather than a measure of integrated exposure.

25010317 96

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Cotinine in saliva, blood, and urine is the most widely accepted biomarker for integrated exposure to MS or ETS (NRC, 1986; U.S. DHHS, 1986). Cotinine is the major metabolite of nicotine, is specific to tobacco, and has a longer half-life for elimination from the body. The elimination half-life in smokers is approximately 20 hours (range of 10 to 37 hours), while it is typically longer in nonsmokers with ETS exposure, particularly in children (Figure 3-11) (Elliot and Rowe, 1975; Collier et al., 1990; Goldstein et al., 1987; Etzel et al., 1985; Greenberg et al., 1984). The longer half-life of cotinine makes it a good indicator of integrated ETS exposure over the previous day or two. Laboratory studies of nonsmokers exposed to acute high levels of ETS over varying times have shown significant uptake of nicotine by the nonsmokers and increases in their cotinine levels (NRC, 1986; U.S. DHHS, 1986; Hoffmann et al., 1984; Russell and Feyerabend, 1975).

Several studies have been conducted of cotinine levels in free-living populations of smokers, nonsmokers reporting passive smoke exposure, and nonsmokers reporting no passive smoke exposure (NRC, 1986; U.S. DHHS, 1986; Greenberg et al., 1984; Wald et al., 1984; Wald and Ritchie, 1984; Jarvis, et al., 1985; Coultas et al., 1987; Riboli et al., 1990; Cummings et al., 1990). These studies have found that exposure to ETS is highly prevalent even among those living with a nonsmoker (e.g., Cummings et al., 1990). Saliva, serum, and urine cotinine levels in ETS-exposed nonsmokers were generally found to be higher than those in nonsmokers reporting no ETS exposure, and levels of cotinine in smokers are considerably higher than those levels in nonsmokers passively exposed (Table 3-5). Cotinine levels in nonsmokers exposed to ETS are on the order of approximately 1% of the levels in active smokers. Cotinine levels of nonsmokers have been found to increase with self-reported ETS exposure (Figures 3-12 and 3-13).

In a 10-country study of ETS exposure of 1,369 nonsmoking women (Riboli et al., 1990), average urinary levels of cotinine/creatinine by country ranged from approximately 2.5 ng/mg for Shanghai to approximately 14 ng/mg for Trieste. Eighty percent of those women sampled had a detectable level of cotinine. Statistically significant differences were observed between centers, with the lowest values observed in Honolulu, Shanghai, and Chandigarh and the highest values in Trieste, Los Angeles, and Athens. This study also found a linear increase in cotinine/creatinine levels for the group of women reporting no ETS exposure either at home or work to the group reporting ETS exposure both at home and at work (Figure 3-14). Urinary cotinine levels were also found to increase with the number of questionnaire-reported passive smoke exposures in a group of 663 persons who never smoked and ex-smokers (Cummings et al., 1990). In that study, 76% of the subjects reported passive smoke exposure, with 27% reporting exposure at home and

250103797

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

28% reporting exposure at work. Jarvis et al. (1983) studied the increase of cotinine in 7 nonsmokers after 2 hours' exposure to ETS in a "smoky public house." They found highly statistically significant increases of cotinine in all body fluids: from 1.1 to 7.3 ng/mL in plasma, from 1.5 to 8.0 ng/mL in saliva, and from 4.8 to 12.9 ng/mL in urine. Because the samples were taken immediately post-exposure, they do not indicate peak cotinine concentrations, however.

Cotinine values in smokers and nonsmokers measured in either the laboratory or field setting show considerable variability attributable to individual differences in the uptake distribution, metabolism, and elimination of nicotine. An additional issue that has to be considered in interpreting the field data is that exposure status is determined by respondent self-reporting. This can lead to a misclassification error, which tends to reduce the differences in cotinine levels measured in the ETS-exposed versus non-ETS-exposed groups and to increase the variability in the levels within any exposure category. Within the exposed group, this misclassification error could either increase or decrease the average cotinine levels measured.

It is important to recognize that nicotine and cotinine are actually proxy biomarkers. They may not be the active agents in eliciting the adverse effect under study but merely indicative of the level of passive smoke exposure. Using these measures to estimate cigarette equivalents or to determine equivalent active smoking exposure could result in over- or underestimating exposure to individual or classes of compounds that may be more directly related to the health or nuisance effect of concern. The use of different biomarker proxies (e.g., protein adducts) could result in estimates of much larger cigarette equivalent doses.

Nicotine and cotinine levels in ETS-exposed nonsmokers measured in laboratory and field studies have been used to estimate cigarette equivalent exposures and to equate ETS exposures with active smoker exposures (NRC, 1986; U.S. DHHS, 1986; Jarvis, 1989). On an equivalent cigarette basis, an upper-bound estimate of nicotine dose of 2.5 mg per day for passive smoke exposure has been proposed (Jarvis, 1989). This would translate into the equivalent of about one-fifth of a cigarette per day, or about 0.7% of the average smoker's dose of nicotine (cigarette equivalent dose of other toxins or carcinogens would be different, as described above). Comparisons of cotinine values in ETS-exposed nonsmokers with those measured in smokers ranged from 0.1% to 2%. One analysis proposed that, on average, nonsmokers' cotinine levels are 0.5% to 0.7% of those found in cigarette smokers (Jarvis, 1989). It should be noted that these estimations are based on a number of assumptions that may not hold (e.g., the half-life of nicotine and cotinine in smokers and nonsmokers is the same).

250103798

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

One of the protein adducts that has been used as a biomarker of active and passive smoking is the 4-aminobiphenyl adduct of hemoglobin (4-ABP-Hb). One advantage of hemoglobin adducts is that their half-life is quite long, and they will persist through the life of a red blood cell, which is approximately 120 days. Therefore, levels of 4-ABP-Hb reflect exposures over the past several weeks, rather than the day or two of exposure-integration reflected by cotinine measurements.

Tobacco smoke is the primary environmental source of 4-aminobiphenyl (its use in the dye industry was discontinued decades ago), and smokers have between five and eight times as much 4-ABP-Hb adducts as nonsmokers (Hammond et al., 1990; Perera et al., 1987; Maclure et al., 1989). That nonsmokers appear to have approximately 10% to 20% the adduct level as smokers may at first appear to be contradictory to the urinary cotinine ratios of about 1%, but in fact both results are quite consistent with our knowledge of the emissions of various contaminants in MS and SS. Approximately twice as much nicotine is emitted in SS as in MS, but about 31 times as much 4-ABP is emitted in SS as in MS. Thus, compared to MS, SS is 15 times more enriched in 4-ABP than in nicotine. The ratio of biomarkers in those exposed to ETS compared to smokers is 15 times greater for the biomarker 4-ABP-Hb than for the biomarker cotinine, a metabolite of nicotine.

The above discussions indicate that the "cigarette equivalent" dose of those exposed to ETS varies with the compound, so that a passive smoker may receive 1% as much nicotine as an active smoker but 15% as much 4-ABP. These commentaries on the data are preliminary and warrant further investigation, but they do suggest the importance of careful interpretation of biomarkers in estimating dose.

3.3.4. Questionnaires for Assessing ETS Exposures

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective studies of acute and chronic effects and in prospective studies. They are the least expensive method of obtaining ETS exposure information for large populations. They can be used to provide a simple categorization of ETS exposure, to determine time-activity patterns of individuals (e.g., how much time is spent in environments where smoking occurs), and to acquire information on the factors or properties of the environment affecting ETS concentrations (e.g., number of cigarettes smoked, size of indoor environments, subjective evaluation of level of smokiness). The time-activity pattern information is combined with measured or estimated concentrations of ETS in each environment to provide an estimate of total exposure. Information

250103799

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

on the factors affecting ETS concentrations is used to model or predict ETS levels in those environments.

Questionnaires are used most extensively to provide a simple categorization of potential ETS exposure (e.g., Do you live with a smoker? Are you exposed to ETS at your place of work? How many hours a week are you exposed to ETS?) and to obtain information on possible confounders (e.g., occupational history, socioeconomic status). When used simply to determine a dichotomous exposure (ETS exposed vs. unexposed), any misclassification tends to bias measures of association toward the null. Thus, any effect that may be present will be underestimated or may even be undetectable. If there are more than two exposure categories (e.g., light, medium, or heavy exposure), the intermediate categories of exposure may be biased either away from or toward the null. Misclassification errors may arise from respondents' lack of knowledge, biased recall, memory failure, or intentional alteration of information. In addition, there are investigator-based sources of misclassification. Errors may arise if semiquantitative levels are incorrectly imputed to answers; for example, even if house exposures are higher than occupational exposures, on average, for any given individual, the ranking may well be reversed from that of the average.

In using questionnaires to assess exposure categories to ETS to determine time-activity patterns and to acquire information on the factors affecting concentrations, it is important to minimize the uncertainty associated with the estimate and to characterize the direction and magnitude of the error.

Unlike those for active smoking, standardized questionnaires for assessing ETS exposures in prospective or retrospective studies of acute or chronic health or nuisance effects do not exist. Questionnaires used to assess ETS exposure have typically not been validated. There is no "gold standard" with which to validate the questionnaire. Various strategies, however, have been used to assess the validity of diverse types of questionnaires used to assess ETS exposure. Efforts to validate questionnaires have used survey data, air monitoring of nicotine in various microenvironments, and nicotine or cotinine in body fluid samples.

One report (NRC, 1986) estimated an error rate of 5% in using surrogate responses in the simple classification of an individual as ever/never smoked. Such a classification scheme (e.g., married to a smoker) has been used to assess a nonsmoking spouse's exposure in the home for ETS-associated cancer outcome. A recent study (Leaderer and Hammond, 1991) of 96 homes using a questionnaire to assess residential smoking and a passive nicotine air monitor found that 13% of the residences reporting no smoking had measurable levels of nicotine, while 28% of the

2501031800

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

residences reporting smoking had nondetectable levels of nicotine. A good level of agreement between questionnaire-reported number of cigarettes smoked and residential levels of ETS-related RSP and nicotine was observed in this study (Figure 3-10).

Studies (Hammond et al., 1989; Schenker et al., 1990; Coultas et al., 1987; Riboli et al., 1990; Cummings et al. 1990; Coultas et al., 1990a) comparing various measures of ETS exposure (e.g., location of exposure, intensity of exposure, duration of exposure, number of cigarettes smoked) with cotinine levels measured in physiological fluids generally meet with only moderate success (explained variations on the order of 40% or less). The largest such study (Riboli et al., 1990) was a collaborative effort conducted in 10 countries; correlations in the range of 0.3 to 0.51 ($p < 0.01$) were found between urinary cotinine levels and various measures of exposure derived from questionnaire data. Using cotinine as a biomarker of exposure, studies indicated that a substantial percentage of those persons reporting no ETS exposure by questionnaire do have measurable exposure. Differences in the uptake metabolism and excretion of nicotine among individuals make it difficult to use this measure as a "gold standard" in validating questionnaires. Also, the recent exposure lasting 1 to 2 days that is measured by cotinine may differ from usual exposure.

In one effort to develop a validated questionnaire (Schenker et al., 1990), 53 subjects were asked detailed questions about their exposures to ETS, including location of exposures, number of smokers, ventilation characteristics, number of hours exposed, proximity of smokers, and intensity of ETS. They then wore a passive sampler for nicotine for 7 days and recorded the same information regarding each exposure episode in daily diaries. Formulae were developed to score the exposures on both the questionnaire and the diary, and these scores were then correlated to the average nicotine concentrations measured over the 7-day period. Excellent correlation was found ($r^2 = 0.83$ for the questionnaire and 0.90 for the diary). However, the simple questions that have most frequently been used in epidemiologic studies (e.g., whether a subject lived with a smoker, number of hours the subject was exposed) were not nearly as well correlated with the measured exposures. These results indicate that reliable questionnaires can be developed but that those used in most studies in the past will lead to some random misclassification of exposure and, hence, underestimation of any effect that may be present.

ETS exposures take place across a number of environments, with an individual's total exposure a function of the amount of time spent in each environment and the concentration in that environment. Questionnaires need to assess exposures across indoor environments. Personal air monitoring or the measurement of a biomarker provides a method to validate ETS exposure

2501031801

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

assessment questionnaires and to assess the contribution of each environment to total current exposure.

Personal air monitoring and cotinine measurements in combination with questionnaires have highlighted the importance of obtaining information on spouses' smoking status, smoking at home, smoking at work, smoking in various other indoor environments (e.g., social settings, vehicles, public places) amount of time in environments where smoking occurs, and the intensity of the exposure (Hammond et al., 1989; Schenker et al., 1990; Coultas et al., 1987; Riboli et al., 1990; Cummings et al. 1990; Coultas et al., 1990a).

3.4. MODELS FOR ASSESSING ETS EXPOSURE

Epidemiologic studies of ETS ideally should have direct measurements of the ETS exposures for the target individuals or populations. It is, however, neither practical nor possible in most instances to obtain such measurements. For example, in retrospective studies of lung cancer or respiratory illnesses, air samples of contaminant levels in various microenvironments or personal air sampling cannot be obtained. Current measurements may not be directly relevant because exposures have changed over the past 20 years. In such cases, past and present ETS exposures can be modeled. Models that predict ETS concentrations in various microenvironments can be used either to estimate total exposure in combination with time-activity patterns or to estimate the impact of variations in factors (e.g., number of cigarettes smoked, changes in ventilation rates) that have an impact on microenvironmental concentrations. Models used for predicting ETS concentrations in indoor spaces will be discussed here.

Predictive or exploratory models for indoor concentrations of ETS-associated air contaminants are generally either physical/chemical or statistical in nature. The physical/chemical model usually follows some form of the general mass balance equation. This approach requires detailed information on the input parameters (e.g., ETS source strengths, infiltration rates, mixing, reaction rates) to predict the indoor concentrations. The input parameters are either measured in chamber studies and in homes or are estimated. This approach has been extensively utilized in chamber studies of ETS-associated air contaminants (Repace and Lowrey, 1980; Hoegg, 1972; Leaderer et al., 1984). In one report, the mass balance equation was used to estimate the range of indoor concentrations of RSP associated with ETS over a range of assumptions related to the input parameters (NRC, 1986). The results of that effort are shown in Figures 3-15 and 3-16. (These figures were taken directly from NRC, 1986.) Figures 3-15 and 3-16 allow for the easy calculation of RSP mass from ETS in indoor environments for a range of conditions. These

2501031802

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

figures highlight the large impact of tobacco combustion on indoor RSP levels and indicate that variations in input parameters (e.g., smoking occupancy) can have substantial impacts on predicted RSP levels.

The mass balance model in its original form requires the measurement or estimation of a number of parameters and, hence, is not easily applied to field studies. A condensed version of the mass balance equation for estimating ETS-generated RSP levels in a variety of indoor microenvironments has been developed by using known emission rates of RSP for tobacco combustion in combination with data from several sources, including both measured and estimated parameters (e.g., RSP emission rates, smoking densities, infiltration or ventilation rates, deposition rates)(Leaderer, 1988). The condensed model is given by:

$$C_{eq} = K(D_{hs}/N_v)$$

where: C_{eq} is the equilibrium RSP concentration in a space due to smoking in $\mu g/m^3$; D_{hs} = the number of active smokers (burning cigarettes) per 100 m^3; N_v is the infiltration/ventilation rate for the space in air changes per hour; and K is calculated from standard conditions (smoking rates, RSP emission rates, mixing rates, ventilation rates, and particle loss rates to surfaces) and is equal to 217 for spaces with three or more smokers, 145 for two smokers, and 72 for one smoker (Repace, 1987). The authors of this approach are currently modifying the model to incorporate nicotine measurements (Repace and Lowrey, in preparation). This simplified model offers an easy method to estimate exposures to RSP-associated ETS. While the model has not been fully validated, it does offer an easy method by which RSP-associated ETS in various indoor spaces can be easily estimated.

The second modeling approach is statistical in nature and based on empirical measurements. These models make simple assumptions with little or no transformations of the independent input variables to the model. The statistical models use, as input parameters, data obtained in large field studies through both measurement and estimation (questionnaires). The statistical models are typically simple linear models where the independent variables are used as they are recorded from the questionnaires to explain variations in the concentrations of the air contaminants measured.

The statistical approach has not been widely used. In a study of 96 homes in New York State (Leaderer and Hammond, 1991), measured weekly levels of RSP and vapor phase nicotine were compared to the number of cigarettes reported smoked (obtained by questionnaire), house

2501031803

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

volume, and measured infiltration rates. Respondent-reported number of cigarettes predicted both residential RSP and vapor phase nicotine-associated ETS levels very well (Figure 3-10). The inclusion of house volume and infiltration rate as independent variables in the models occasionally proved to be significant at the 0.05 level, but it explained only a small amount of the variation in the model between measured RSP and nicotine levels.

3.5. SUMMARY

Environmental tobacco smoke is a major source of indoor air contaminants. The ubiquitous nature of ETS in indoor environments indicates that some unintentional inhalation of ETS by nonsmokers is unavoidable. Environmental tobacco smoke is a dynamic complex mixture of more than 4,000 chemicals found in both vapor and particle phases. Many of these chemicals are known toxins and carcinogenic agents. Nonsmoker exposure to ETS-related toxic and carcinogenic substances will occur in indoor spaces where there is smoking occupancy. Many of the ETS compounds are emitted in higher concentrations in sidestream smoke than mainstream smoke. Sidestream emissions, however, are quickly diluted into the environment where ETS exposures take place. Individuals close to smokers (e.g., an infant in a smoking parent's arms) may be directly exposed to the plume of sidestream smoke or exhaled mainstream smoke and thus be more heavily exposed.

Given the complex nature of ETS, it is necessary to identify marker or proxy compounds that, when measured, will allow for the quantification of exposure to ETS. Vapor phase nicotine and respirable suspended particle mass are two such markers that are suitable indicators of exposure to ETS. Nicotine and RSP have been measured in personal monitoring studies and in studies of a variety of indoor environments. The results of these studies clearly demonstrate that reported exposure to ETS, even under the conditions of low frequency, duration, and magnitude, will result in RSP and nicotine values above background levels. These studies indicate that ETS exposures take place in a wide range of microenvironments (e.g., residences, workplaces, restaurants, airplanes) where smoking occurs. Indoor levels of RSP and vapor phase nicotine have been shown to vary in a linear fashion with reported tobacco consumption. Nicotine levels measured indoors have ranged from less than 1 $\mu g/m^3$ to more than 500 $\mu g/m^3$, while RSP-associated ETS levels have ranged from less than 5 $\mu g/m^3$ to more than 1 mg/m^3. Nicotine exposures greater than 100 $\mu g/m^3$ are exceedingly rare; most environments measured have ranged from less than 0.3 $\mu g/m^3$ (smoke free) to 30 $\mu g/m^3$; bars and smoking sections of planes may reach

2501031804

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

50 to 75 $\mu g/m^3$. Thus, the normal range of ETS exposures is approximately hundredfold: 0.3 to 30 $\mu g/m^3$ for nicotine and from 5 to 500 $\mu g/m^3$ for RSP.

In residences with smoking occupancy, average daily or weekly nicotine values might typically range from less than 1 to 10 $\mu g/m^3$, varying principally as a function of number of smokers or number of cigarettes smoked. Average daily or weekly residential concentrations of ETS-associated RSP could be expected to increase from 18 to 95 $\mu g/m^3$ (added to background levels) in homes where smoking occurs. Like nicotine, ETS-associated RSP increases with increased smoking. Average levels of nicotine and RSP in offices with smoking occupancy are roughly comparable to those in homes.

Cotinine in saliva, blood, and urine is the most widely accepted biomarker of ETS exposure. It is not directly related to the air exposure to nicotine because of substantial differences in the time course of exposure uptake, metabolism, and elimination of nicotine in exposed individuals. In addition, the ratio of cotinine in smokers versus nonsmokers may not be the same as the ratio for the active agents in ETS responsible for the adverse effects. Cotinine, however, is an excellent indicator that ETS exposure has taken place and may be a good indicator of dose. The available data indicate that as many as 80% of nonsmokers are exposed to ETS, that there is variability in average exposure levels among different cities, and that cotinine levels vary as a function of passive smoke exposure. Comparisons of cotinine levels in smokers and ETS-exposed nonsmokers have led to estimates that nonsmokers receive from 0.1% to 7% of the dose of nicotine of an average smoker. The dose of active agents may be quite different (e.g., nonsmokers may receive 10% to 20% of the dose of 4-ABP that smokers inhale). These estimates, however, are based on a number of assumptions that may not hold.

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective studies of acute and chronic effects and in prospective studies. They have been used not only to establish simple categories of ETS exposure, but also to obtain information on activity patterns of exposed individuals and to obtain information on environmental factors affecting concentrations in different indoor environments. No standardized or validated questionnaires have yet been developed for assessing ETS exposure. A number of studies have compared questionnaire responses to measured air concentrations of nicotine and RSP and cotinine levels. These efforts have indicated that a significant percent of individuals reporting no exposure had actually been exposed. In general, questionnaires had moderate success in assessing exposure status and level of exposure. Misclassification errors must be addressed in using questionnaires to assess ETS exposure.

250103180S

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Physical/chemical and statistical models provide a viable means for predicting concentrations of ETS-related contaminants in situations when it is impractical to obtain direct measurements. The utility of these models will be enhanced when they are better validated.

Environmental tobacco smoke represents an important source of indoor air contaminants. The available data suggest that exposure to ETS is widespread with a wide range of exposure levels.

2501031806

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 3-1. Distribution of constituents in fresh, undiluted mainstream smoke and diluted sidestream smoke from nonfilter cigarettes[1]

Constituent	Amount in MS	Range in SS/MS
Vapor phase:[2]		
Carbon monoxide	10-23 mg	2.5-4.7
Carbon dioxide	20-40 mg	8-11
Carbonyl sulfide	12-42 μg	0.03-0.13
Benzene[3]	12-48 μg	5-10
Toluene	100-200 μg	5.6-8.3
Formaldehyde[4]	70-100 μg	0.1-~50
Acrolein	60-100 μg	8-15
Acetone	100-250 μg	2-5
Pyridine	16-40 μg	6.5-20
3-Methylpyridine	12-36 μg	3-13
3-Vinylpyridine	11-30 μg	20-40
Hydrogen cyanide	400-500 μg	0.1-0.25
Hydrazine[4]	32 ng	3
Ammonia	50-130 μg	3.7-5.1
Methylamine	11.5-28.7 μg	4.2-6.4
Dimethylamine	7.8-10 μg	3.7-5.1
Nitrogen oxides	100-600 μg	4-10
N-Nitrosodimethylamine[4]	10-40 ng	20-100
N-Nitrosodiethylamine[4]	ND-25 ng	<40
N-Nitrosopyrrolidine[4]	6-30 ng	6-30
Formic acid	210-490 μg	1.4-1.6
Acetic acid	330-810 μg	1.9-3.6
Methyl chloride	150-600 μg	1.7-3.3

(continued on the following page)

2501031807

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 3-1. (continued)

Constituent	Amount in MS	Range in SS/MS
Particulate phase:[2]		
Particulate matter[8]	15-40 mg	1.3-1.9
Nicotine	1-2.5 mg	2.6-3.3
Anatabine	2-20 μg	<0.1-0.5
Phenol	60-140 μg	1.6-3.0
Catechol	100-360 μg	0.6-0.9
Hydroquinone	110-300 μg	0.7-0.9
Aniline[4]	360 ng	30
2-Toluidine	160 ng	19
2-Naphthylamine[3]	1.7 ng	30
4-Aminobiphenyl[3]	4.6 ng	31
Benz[*a*]anthracene[5]	20-70 ng	2-4
Benzo[*a*]pyrene[4]	20-40 ng	2.5-3.5
Cholesterol	22 μg	0.9
γ-Butyrolactone[5]	10-22 μg	3.6-5.0
Quinoline	0.5-2 μg	3-11
Harman[6]	1.7-3.1 μg	0.7-1.7
N'-Nitrosonornicotine[5]	200-3,000 ng	0.5-3
NNK[7]	100-1,000 ng	1-4
N-Nitrosodiethanolamine[4]	20-70 ng	1.2
Cadmium[4]	110 ng	7.2
Nickel[3]	20-80 ng	13-30
Zinc	60 ng	6.7
Polonium-210[3]	0.04-0.1 pCi	1.0-4.0
Benzoic acid	14-28 μg	0.67-0.95
Lactic acid	63-174 μg	0.5-0.7
Glycolic acid	37-126 μg	0.6-0.95
Succinic acid	110-140 μg	0.43-0.62

(continued on the following page)

2501031808

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 3-1. (continued)

[1] Data from Elliot and Rowe (1975); Schmeltz et al. (1979); Hoffman et al. (1983); Klus and Kuhn (1982); Sakuma et al. (1983, 1984a,b); Hiller et al. (1982). Diluted SS is collected with airflow of 25 ml/s, which is passed over the burning cone; as presented in the NRC report on passive smoking (1986).

[2] Separation into vapor and particulate phases reflects conditions prevailing in MS and does not necessarily imply same separation in SS.

[3] Known human carcinogen, according to U.S. EPA or IARC.

[4] Probable human carcinogen, according to U.S. EPA or IARC.

[5] Animal carcinogen (Vaino et al., 1985).

[6] 1-methyl-9*H*-pyrido[3,4-*b*]-indole.

[7] NNK = 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone.

[8] Contains di- and polycyclic aromatic hydrocarbons, some of which are known animal carcinogens.

2501031809

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 3-2. Studies measuring personal exposure to airborne nicotine associated with ETS for nonsmokers

Study	Setting	Subject	N	Nicotine, $\mu g/m^3$ X(±SD)	Nicotine, $\mu g/m^3$ Range	Comments
Mattson et al., 1989	Airplane	Attendants	16	4.7 (±4.0)	0.1-10.5	4 attendants on 4 flights
Schenker et al., 1990	Railroad	Clerks	40	6.9		Samples collected over work shifts
Coultas et al., 1990a	Workplace	Nonindustrial	15	20.4 (±20.6)		
Muramatsu et al., 1984	Office	Volunteers	10	21.1		Calculated from data presented
	Laboratory		8	5.8		
	Conference room		5	38.7		
	Home		3	11.2		
	Hospital lobby		1	3.0		
	Hotel lobby		4	11.2		
	Restaurant		15	26.0		
	Transportation		22	21.7		
Muramatsu et al., 1984	Office	Volunteers	3	6.9		Calculated from data presented
	Home		7	7.0		
	Restaurant		15	28.2		
	Car		7	40.0		
	Public transportation		1	11.4		

DRAFT--DO NOT QUOTE OR CITE

2501031810

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 3-3. Studies measuring personal exposure to particulate matter associated with ETS for nonsmokers

Study	Setting	Number of subjects			Particle Mass, $\mu g/m^3$		Particle Mass due to ETS
		Total	No ETS exp.	ETS exp.	X (±SD)	Range	$\mu g/m^3$
Spengler et al., 1981	24hr day	45			NR	NR	20[a]
Spengler et al., 1985	24hr day	101			NR	NR	
			28		NR	NR	28[a]
				73	NR	NR	
Sexton et al., 1984	24hr day	48			NR	NR	
			NR		31.7	NR	18.4[a]
				NR	50.1	NR	
Coultas et al., 1990a	Workplace	15			63.9±41.5	4.0-145.8	
			1		4.0		64[b]
				14	68.2±39.5	14.7-145.8	
Schenker, 1990	Workplace				86		c

a = Calculated by authors from the regression line.
b = Calculated from data presented, after the method of Leaderer and Hammond (1991).
c = Calculated from nicotine exposure, after the method of Leaderer and Hammond (1991).

NR = Not reported

DRAFT--DO NOT QUOTE OR CITE

25010318 11
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 3-4. Weekly average concentrations of each measure of exposure by parental smoking status in the cross-sectional study, Minnesota, 1989

	Smoking Status				
	Non-smokers	Light smokers	Father only	Mother only	Both parents
Number of subjects	23	4	8	6	7
Total cigarettes (no./week)	0.9	28.8	68.6	58.8	227.6
Activity room nicotine ($\mu g/m^3$)	0.15	0.32	2.45	5.50	12.11
Bedroom nicotine ($\mu g/m^3$)	-	0.30	1.21	2.66	5.32

2501031812

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 3-5. Approximate relations of nicotine as the parameter between nonsmokers, passive smokers, and active smokers[1]

Nicotine/Cotinine	Nonsmokers Without ETS Exposure (N=46)		Nonsmokers With ETS Exposure (N=54)		Active Smokers (N=94)
	Mean Value	% of Active Smokers' Value	Mean Value	% of Active Smokers' Value	Mean Value
Nicotine (ng/ml):					
in plasma	1.0	7.0	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1*	0.7	1,750
Cotinine (ng/ml):					
in plasma	0.8	0.3	2.0*	0.7	275
in saliva	0.7	0.2	2.5**	0.8	310
in urine	1.6	0.1	7.7**	0.6	1,390

[1] Differences between nonsmokers exposed to ETS compared with nonsmokers without exposure: *p<0.01;**p<0.001.

Source: Jarvis, 1987.

DRAFT--DO NOT QUOTE OR CITE

2501031813

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

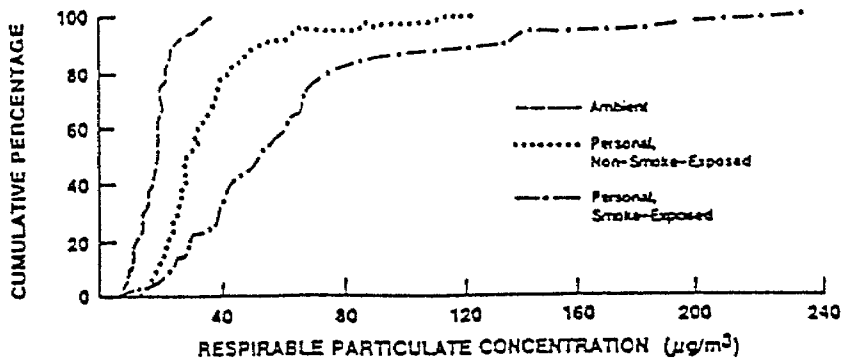
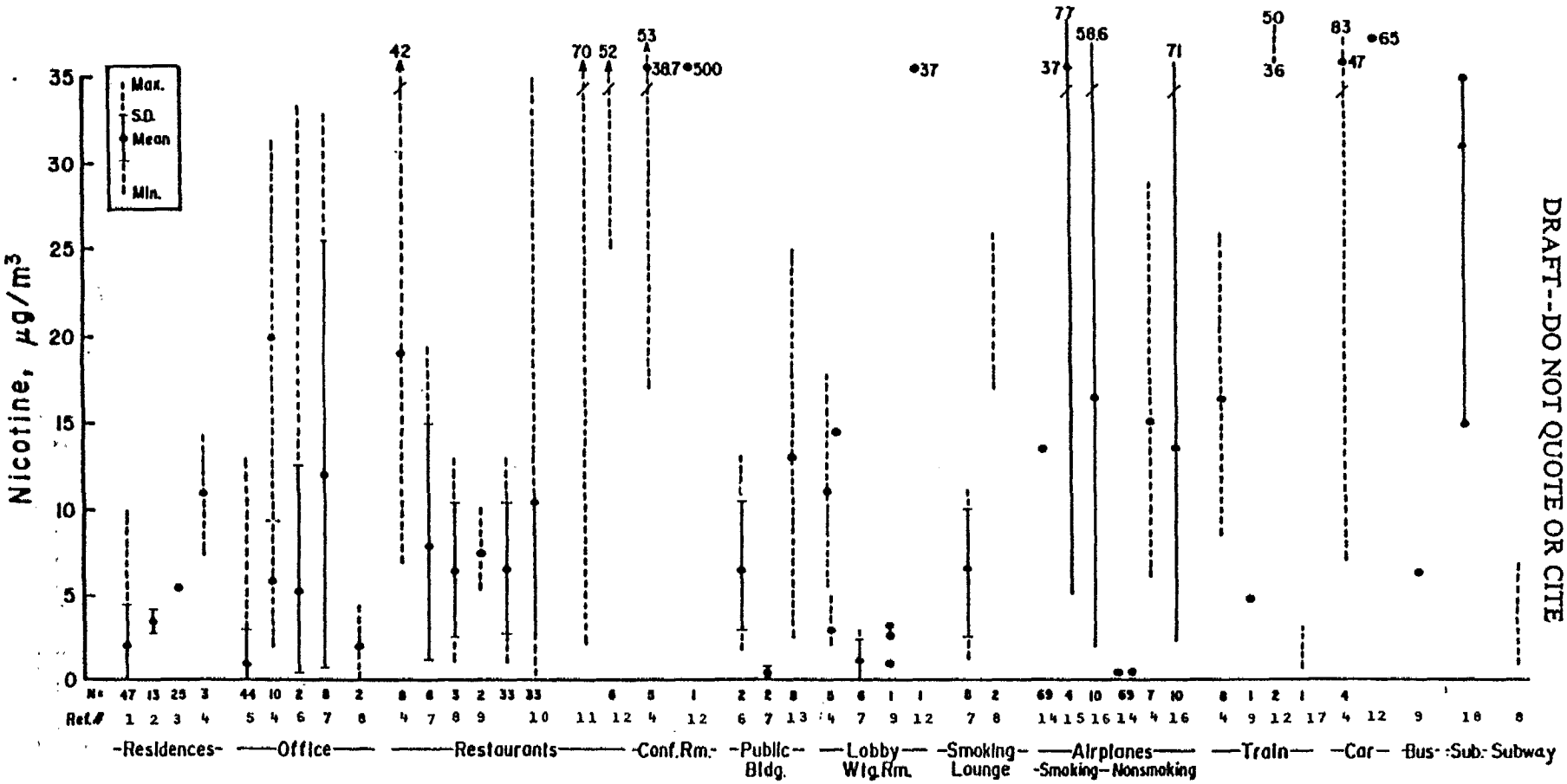


Figure 3-1. Cumulative frequency distribution of respirable suspended particle (RSP) mass concentrations from central site ambient and personal monitoring of smoke-exposed and nonsmoke-exposed individuals. Reprinted from Spengler et al., 1985.

05/15/92
2501031814

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000



DRAFT--DO NOT QUOTE OR CITE

2501031815

05/15/92

Figure 3-2. Mean, standard deviation, maximum, and minimum nicotine values measured in different indoor environments with smoking occupancy. References from which observations are reported and the number of environments monitored are also given.

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

REFERENCES FOR FIGURES 3-2 AND 3-4

Figure 3-2

1 NRC, 1986
2 U.S. DHHS, 1986
3 Brunnemann et al., 1976
4 Wynder and Hoffmann, 1967
5 Dube and Green, 1982
6 Adams, 1987
7 Guerin, 1987
8 Higgins, 1987
9 Leaderer, 1990
10 NRC, 1981
11 Hammond, 1987
12 Eatough et al., 1986
13 Lofroth et al., 1989
14 Eatough et al., 1989
15 Leaderer and Hammond, 1991
16 Benner et al., 1989
17 Hammond et al., 1988
18 Rickert et al., 1984

Figure 3-4

19 Eudy et al., 1985
20 Eatough et al., 1990
21 Hammond, 1987
22 Hammond, 1987
23 Mumford et al., 1989
24 Hammond et al., 1989
25 Marbury, 1990
26 Eatough, 1989
27 Koutrakis et al., 1989
28 DHEW, 1977
29 Muramatsu et al., 1984
30 Oldaker and Conrad, 1987
31 Ogden et al., 1989
32 Leaderer, 1988
33 Repace and Lowrey, 1980
34 Ishizu, 1980
35 Schenker et al., 1990
36 Coghlin et al., 1989
37 Spengler et al., 1981
38 Spengler et al., 1985
39 Sexton et al., 1984
40 Weber, 1980

25010318 16

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

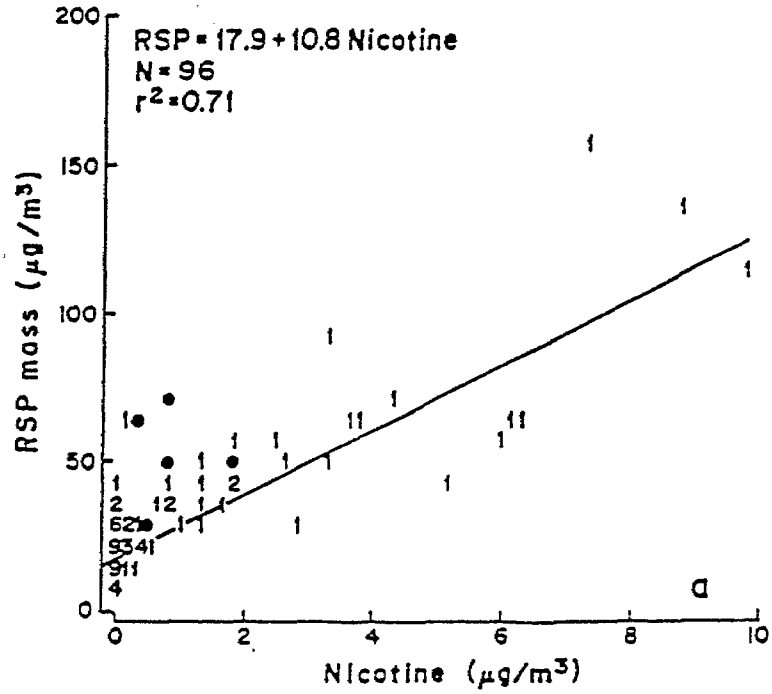


Figure 3-3. Weeklong respirable suspended particle (RSP) mass and nicotine measurements in 96 residences with a mixture of sources. Numbers 1-9 refer to the number of observations at the same concentration. Reprinted from Leaderer and Hammond, 1991.

250103181?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

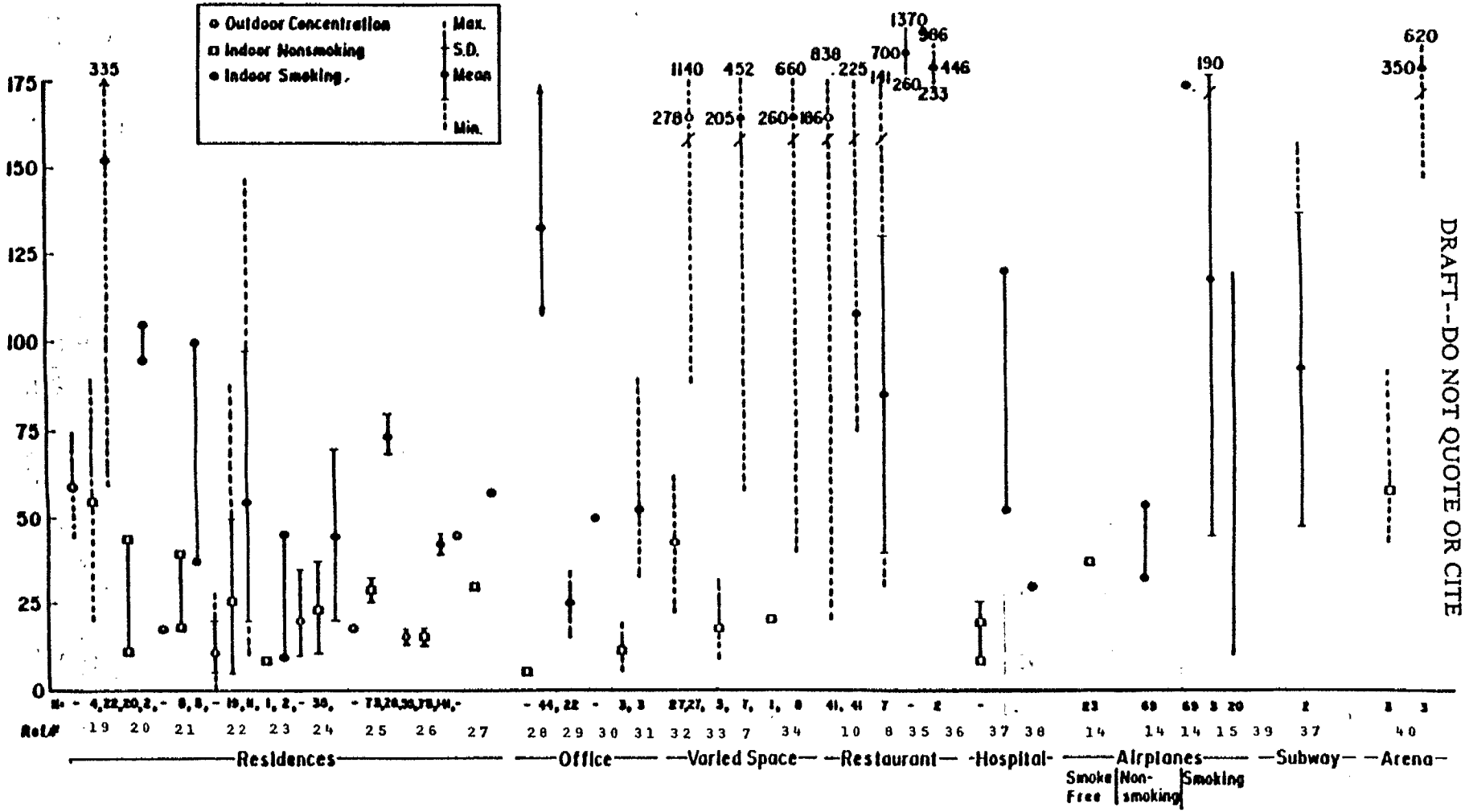


Figure 3-4. Mean, standard deviation, maximum, and minimum concentrations of respirable suspended particle (RSP) mass measured in different indoor environments for smoking and nonsmoking occupancy. Also shown are outdoor concentrations. References from which observations are reported and the number of environments monitored are provided with Figure 3-2.

DRAFT--DO NOT QUOTE OR CITE

250103181B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

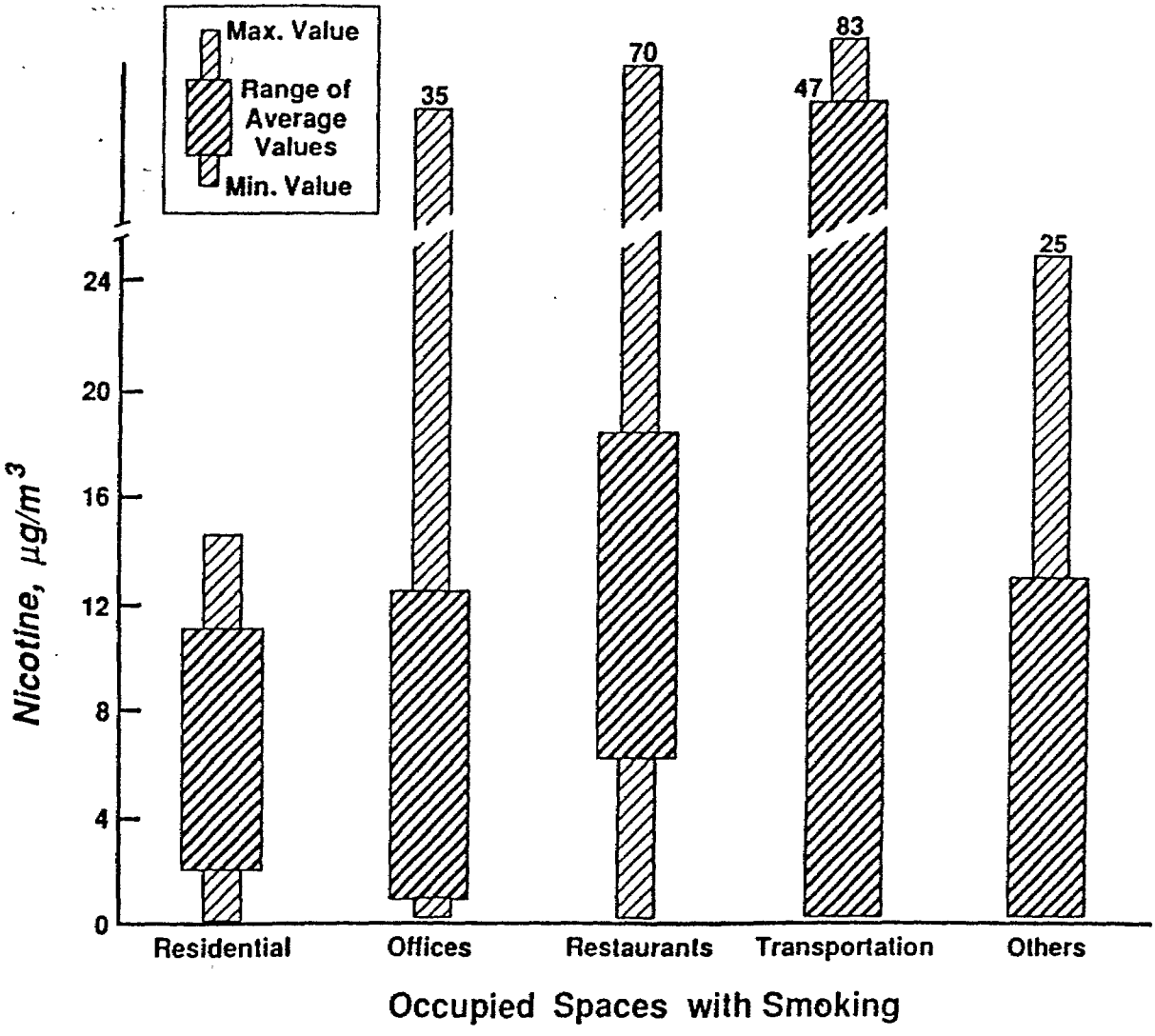


Figure 3-5. Range of average nicotine concentrations and range of maximum and minimum values measured by different indoor environments for smoking occupancy from studies shown in Figure 3-2. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

05/15/92
2501031819

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

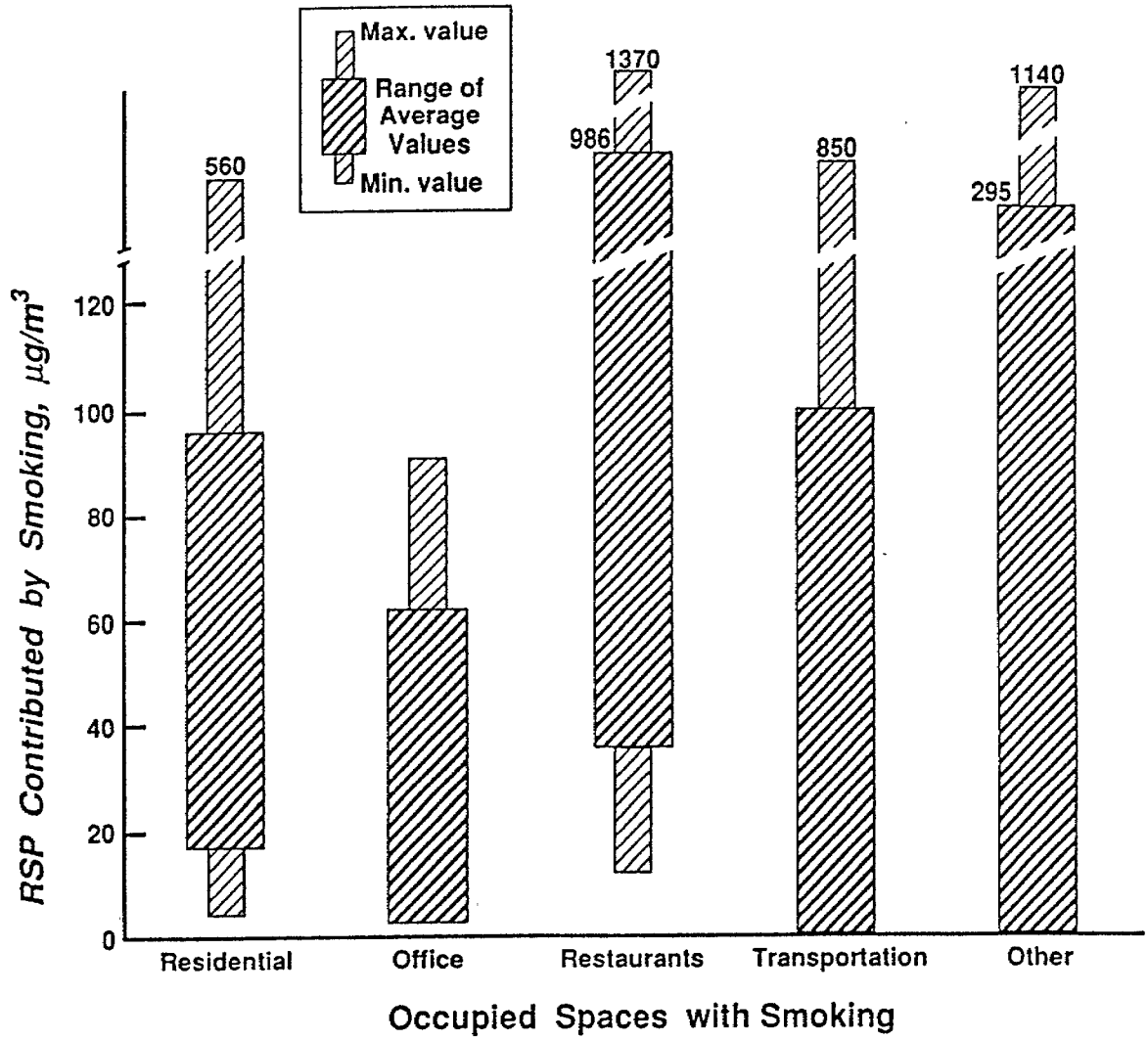


Figure 3-6. Range of average respirable suspended particle (RSP) mass concentrations and range of maximum and minimum values measured by different indoor environments for smoking occupancy from studies shown in Figure 3-4. RSP values represent the contribution to background levels without smoking. Background levels were determined by subtracting reported indoor concentrations without smoking. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

25010318 20

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

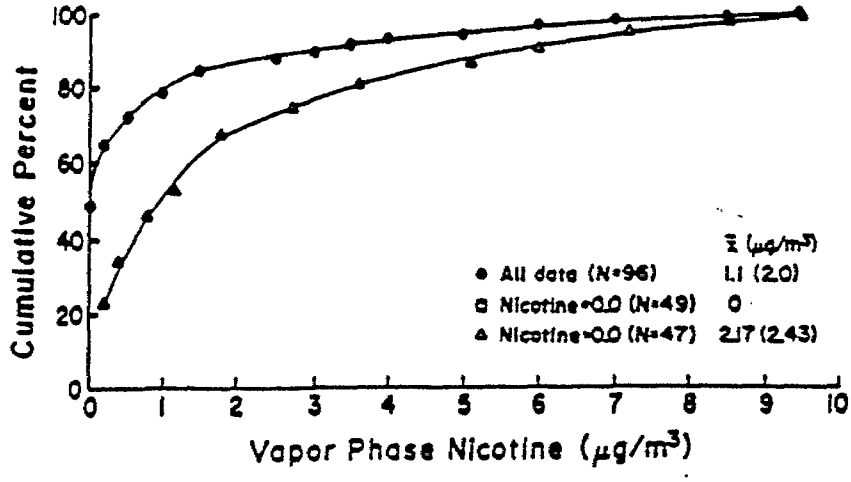


Figure 3-7. Cumulative frequency distribution and arithmetic means of vapor-phase nicotine levels, measured over a 1-week period in the main living area in residences in Onondaga and Suffolk Counties in New York State between January and April 1986. Reprinted from Leaderer and Hammond, 1991.

250103182

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

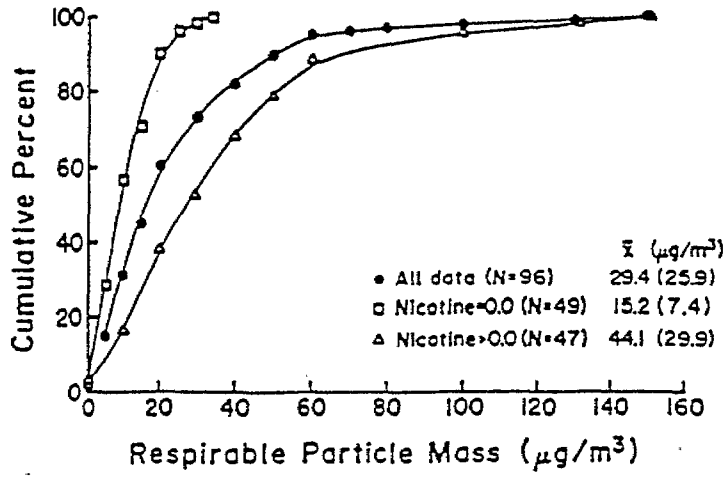


Figure 3-8. Range of average nicotine concentrations and range of maximum and minimum values measured by different indoor environments from studies shown in Figure 3-2. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

2501031822

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

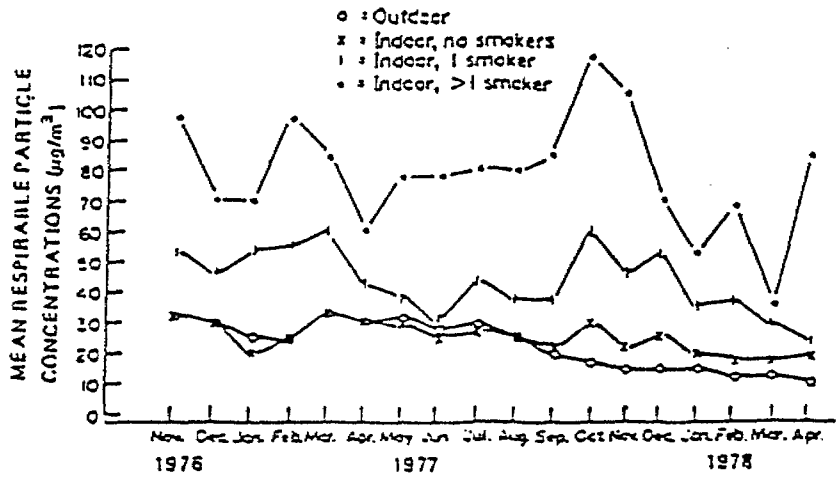
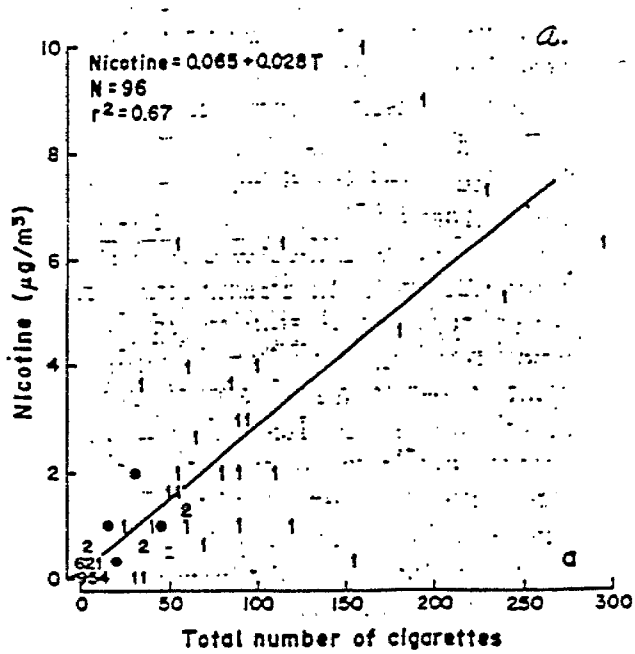


Figure 3-9. Monthly mean respirable suspended particle (RSP) mass concentrations in six U.S. cities. Reprinted from Spengler et al., 1981.

2501031823

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000



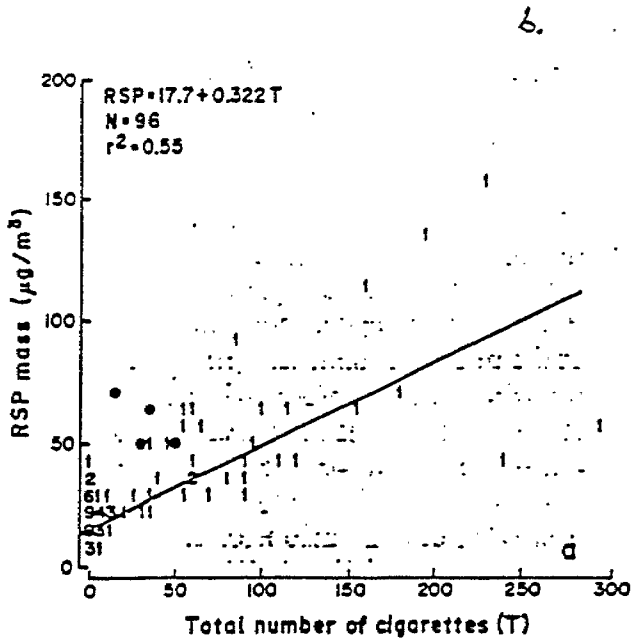


Figure 3-10 a and b. Weeklong nicotine and respirable suspended particle (RSP) mass concentrations, measured in the main living area of 96 residences versus the number of questionnaire-reported cigarettes smoked during the air-sampling period. Numbers 1-9 refer to the number of observations at the same concentrations. Closed circles indicate that cigar or pipe smoking was reported in the houses, with each cigar or pipe smoked set equal to a cigarette. Data from residences in Onondaga and Suffolk counties in New York State between January and April 1986.

250103182

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

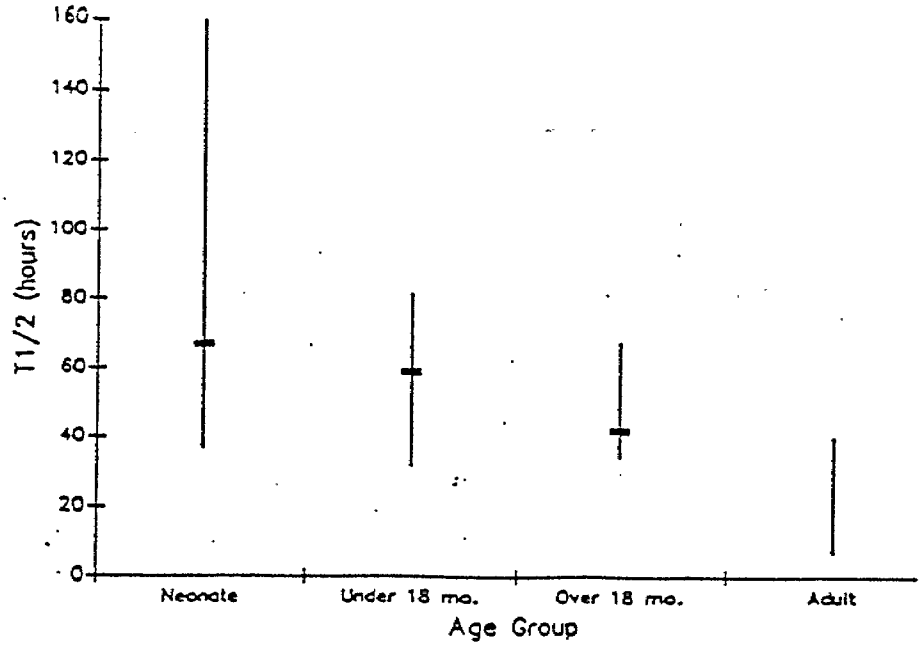


Figure 3-11. Average continue $t_{1/2}$ by age groups. Reprinted from Collier et al., 1990.

250103825

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

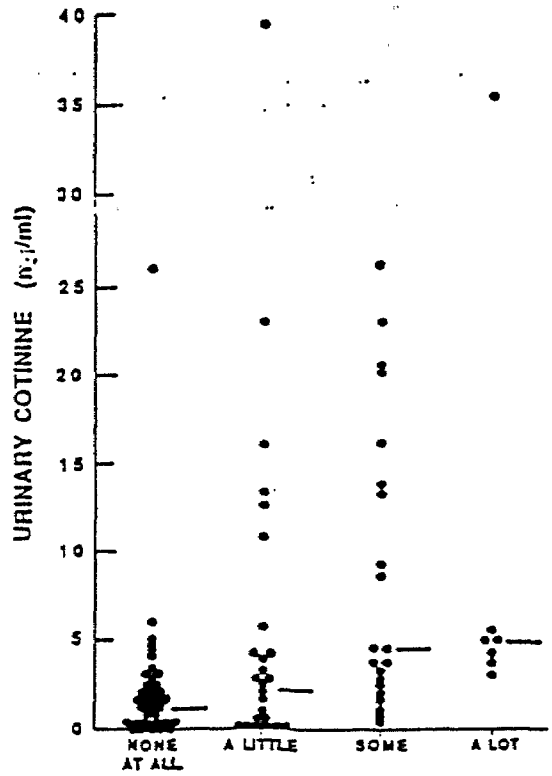


Figure 3-12. Distribution of individual concentrations of urinary cotinine by degree of self-reported exposure to ETS. Horizontal bars indicate median values. Reprinted from Jarvis and Russell[1], 1985.

25010031826

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

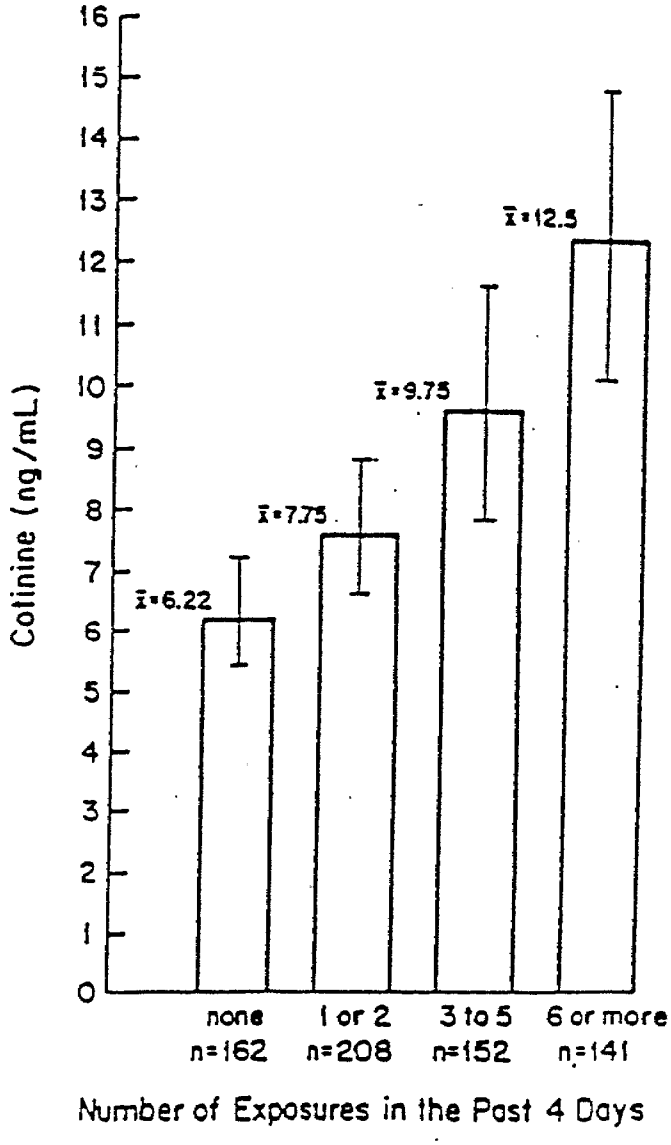


Figure 3-13. Urinary cotinine concentrations by number of reported exposures to tobacco smoke in the past 4 days among 663 nonsmokers, Buffalo, New York, 1986. Reprinted from Cummings et al., 1990.

250103182?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

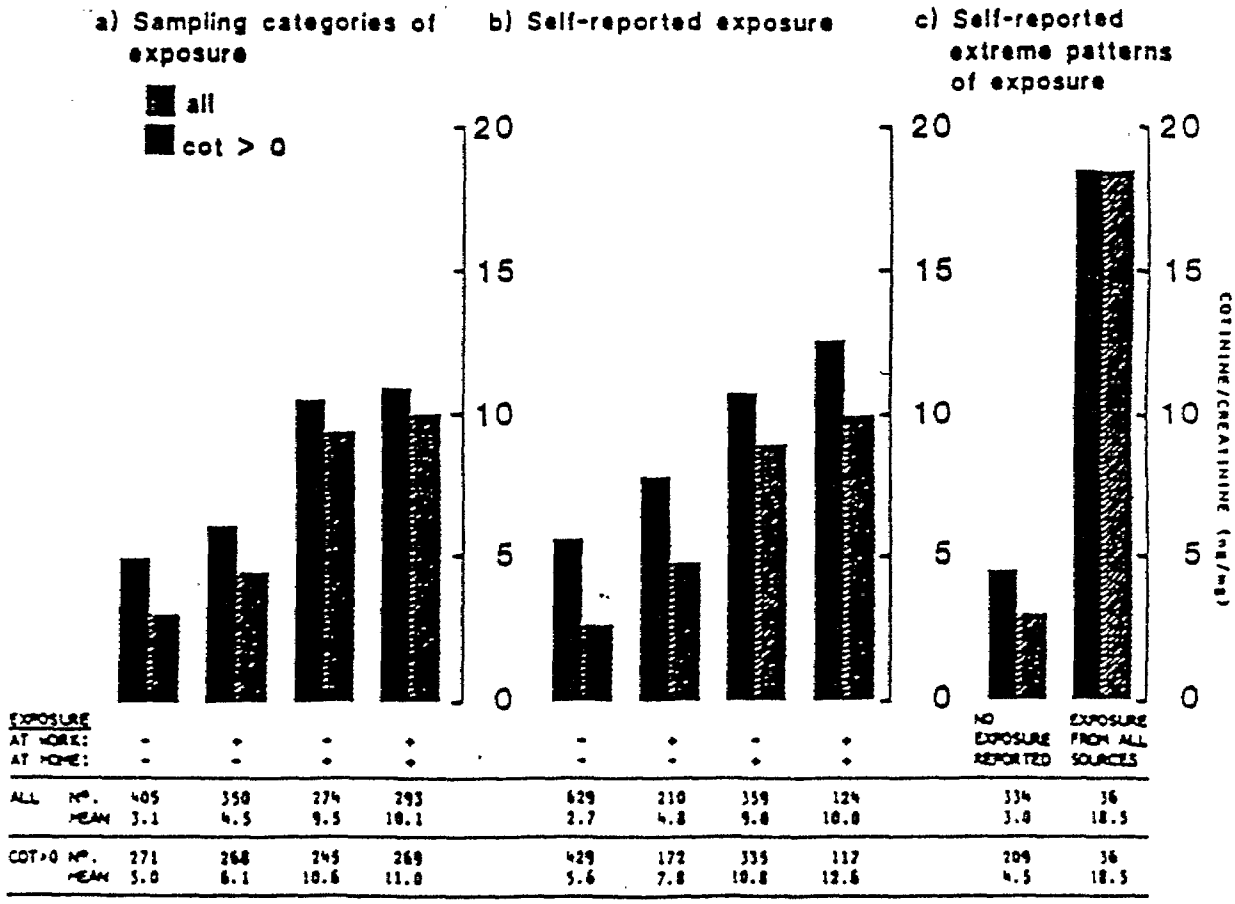


Figure 3-14. Average cotinine/creatinine levels for subgroups of nonsmoking women defined by sampling categories of exposure or by self-reporting exposure to ETS from different sources during the 4 days preceding collection of the urine sample. Reprinted from Riboli et al., 1990.

250103828

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

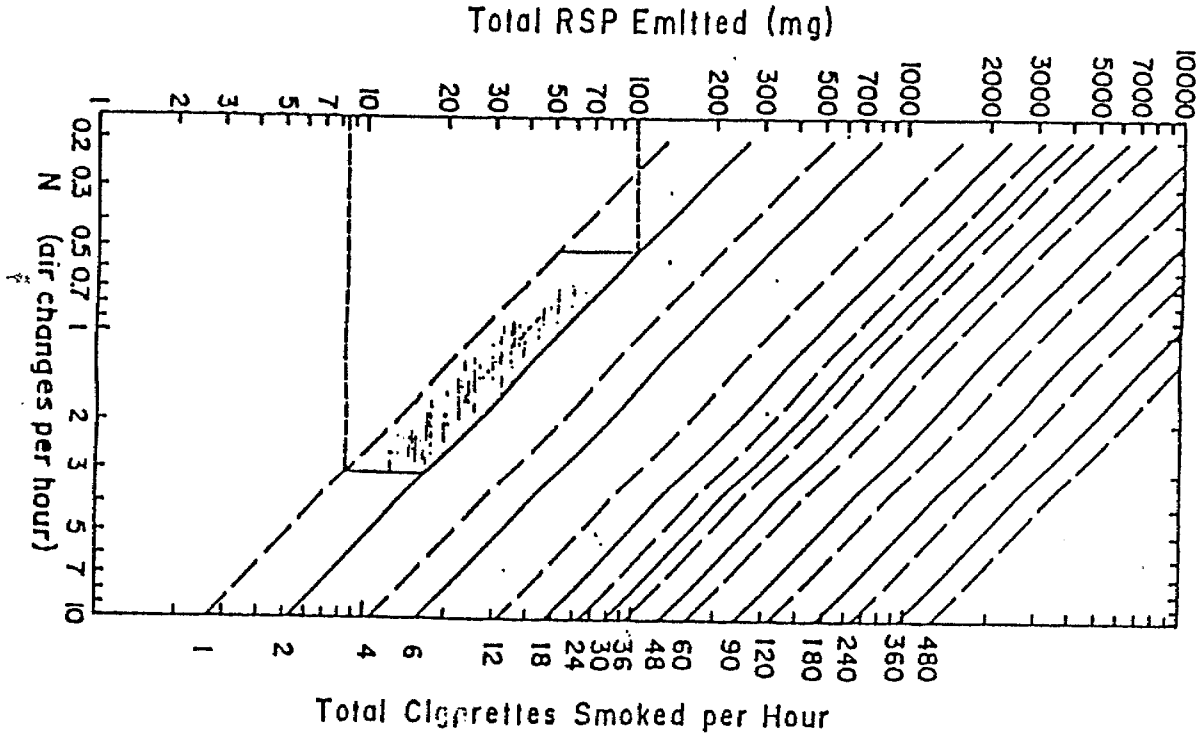


Figure 3-15. Diagram for calculating the respirable suspended particle (RSP) mass from ETS emitted into any occupied space as a function of the smoking rate and removal rate (N). The removal rate is equal to the sum of the ventilation or infiltration rate (n_v) and removal rate by surfaces (N) times the mixing factor m. The calculated ETS-related RSP mass determined from this figure serves as an input to Figure 3-16 to determine the ETS-related RSP mass concentration in any space in ug/m^3. Smoking (diagonal lines) are given as cigarettes smoked per hour. Mixing is determined as a fraction and n_v and n8 are in air changes per hour (ach). All three parameters have to be estimated or measured. Calculations were made using the equilibrium form of the mass-balance equation and assume a fixed emission rate of 26 mg/m^3 of RSP.

Shaded area shows the range of RSP emissions that could be expected for a residence with one smoker smoking at a rate of either 1 or 2 cigarettes per hour for the range of mixing, ventilation, and removal rates occurring in residences under steady-state conditions. Reprinted from NRC (1986).

05/15/92
250103182

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

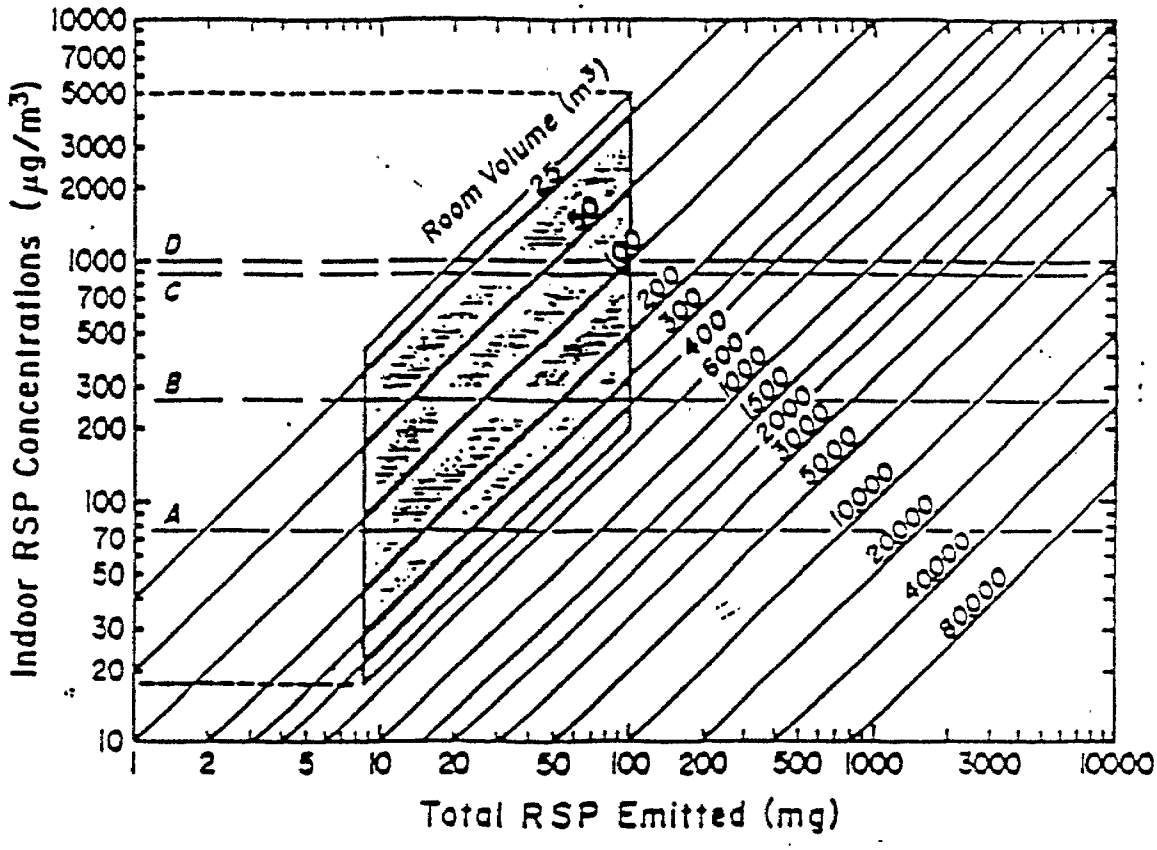


Figure 3-16. Diagram to calculate the ETS-associated respirable suspended particle (RSP) mass concentration in a space as a function of total mass of ETS-generated RSP emitted (determined from Figure 3-15) and the volume of a space (diagonal lines). The concentrations shown assume a background level in the space of zero. The particle concentrations shown are estimates during smoking occupancy. The dashed horizontal lines (A, B, C, and D) refer to National Ambient Air Quality Standards (health-related) for total suspended particulates established by the U.S. Environmental Protection Agency. A is the annual geometric mean. B is the 24-hour value not to be exceeded more than once a year. C is the 24-hour air pollution emergency level. D is the 24-hour significant harm level. Shaded area shows the range of concentrations expected (from Figure 3-15) for a range of typical volumes of U.S. residences and rooms in these residences. Reprinted from NRC (1986).

250103183O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

4. HAZARD IDENTIFICATION I: LUNG CANCER IN ACTIVE SMOKERS, LONG-TERM ANIMAL BIOASSAYS, AND GENOTOXICITY STUDIES

4.1. INTRODUCTION

Numerous epidemiologic studies have conclusively established that the tobacco smoke inhaled from active smoking is a human lung carcinogen (U.S. DHHS, 1982; IARC, 1986). A clear dose-response relationship exists between lung cancer and amount of exposure, without any evidence of a threshold level. It is, therefore, reasonable to theorize that exposure to environmental tobacco smoke (ETS) might also increase the risk of lung cancer in both smokers and nonsmokers. As documented in the previous chapter, the chemical compositions of mainstream smoke (MS) and ETS are qualitatively similar, and both contain a number of known and suspected human carcinogens. In addition, both MS and ETS have been shown to be carcinogens in animal bioassays (Wynder and Hoffman, 1967; Grimmer et al., 1988) and genotoxins in in vitro systems (IARC, 1986). Furthermore, as the previous chapter also describes, exposure assessments of indoor air and measurements of nicotine levels in nonsmokers confirm that passive smokers are exposed to and absorb appreciable amounts of ETS that might result in notable lung cancer risk.

This chapter reviews the major evidence for the lung carcinogenicity of tobacco smoke derived from human studies of active smoking and the key supporting evidence from animal bioassays and in vitro experiments. The evidence from the few animal and mutagenicity studies pertaining specifically to ETS is also presented. The majority of this information has already been well documented by the U.S. Department of Health and Human Services (U.S. DHHS) (1982) and the International Agency for Research on Cancer (IARC) (1986). The current discussion mainly extracts and summarizes some of the important issues and principal studies described in those excellent reports.

In view of the abundant and consistent human evidence establishing the carcinogenic potential of active smoking to the lung, the bulk of this chapter focuses on the human data. Although EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a) suggest an extensive review of all evidence pertaining to carcinogenicity, we believe that the wealth of human cancer studies on both MS and ETS provide the most appropriate database from which to evaluate the lung cancer potential of ETS. Thus, the animal evidence and genotoxicity results are given only limited attention here. Similarly, a discussion of the mutagenicity data for individual smoke components would be superfluous in the context of the overwhelming evidence from other, more

2501031831

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

pertinent sources and is not included. Extensive reviews of these data can be found in the U.S. DHHS (1982) and IARC (1986) publications. Claxton et al. (1989) provide an assessment of the genotoxicity of various ETS constituents.

4.2. LUNG CANCER IN ACTIVE SMOKERS

Studies of active smoking in human populations from many countries provide direct and incontrovertible evidence for a dose-related, causal association between cigarette smoking and lung cancer. This evidence includes time trends in lung cancer mortality rates associated with increasing cigarette consumption, high relative risks for lung cancer mortality in smokers of both sexes observed consistently in numerous independent retrospective and prospective studies, and dose-response relationships demonstrated with respect to smoking intensity and duration and for all four major histological types of lung cancer.

4.2.1. Time Trends

While the overall cancer death rate in the United States has been fairly stable since 1950, the lung cancer death rate has increased drastically for both males and females (Figures 4-1 and 4-2). Age-adjusted lung cancer mortality rates in men have increased from 11 per 100,000 in 1940 to 73 per 100,000 in 1982, leveling slightly to 74 per 100,000 in 1987 (Garfinkel and Silverberg, 1991). In women, lung cancer mortality rates have risen from 6 per 100,000 in the early 1960s to 28 per 100,000 in 1987 (Garfinkel and Silverberg, 1991).

The striking time trends and sex differences seen in lung cancer mortality rates correlate with historical smoking patterns. Increases in lung cancer death rates parallel increases in cigarette consumption with a roughly 20-year lag time, accounting for the latency period for the development of smoking-induced lung cancer. Males started smoking cigarettes in large numbers during the years around World War I, whereas females did not begin smoking in appreciable numbers until World War II. Cigarette consumption per capita (based on the total population age 18 and older) in the United States rose from 1,085 in 1925 to a high of 4,148 in 1973. In the past two decades, cigarette consumption has decreased to 2,888 in 1989 (Garfinkel and Silverberg, 1991). This decline correlates with the leveling off of lung cancer mortality rates in recent years.

2501031832

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

4.2.2. Dose-Response Relationships

More than 50 independent retrospective studies have consistently found a dose-related association between smoking and lung cancer (U.S. DHHS, 1982). Eight major prospective studies from five countries corroborate this association:

- American Cancer Society (ACS) Nine-State Study (white males)
  (Hammond and Horn, 1958a,b)
- Canadian War Veterans Study
  (Best et al., 1961; Lossing et al., 1966)
- British Doctors Study
  (Doll and Hill, 1964a,b; Doll and Peto, 1976; Doll et al., 1980)
- American Cancer Society (ACS) 25-State Study
  (Hammond, 1966; Hammond and Seidman, 1980)
- U.S. Veterans Study
  (Kahn, 1966; Rogot and Murray, 1980)
- California Labor Union Study
  (Weir and Dunn, 1970)
- Swedish Study (sample of census population)
  (Cederlof et al., 1975)
- Japanese Study (total population of 29 health districts)
  (Hirayama, 1967, 1975a,b, 1977, 1978, 1982, 1985)

Details of the designs of these studies are summarized in Table 4-1. These eight studies together represent more than 17 million person-years and more than 330,000 deaths. Lung cancer mortality ratios from the prospective studies are presented in Table 4-2. Combining the data from the prospective studies results in a lung cancer mortality ratio of about 10 for male cigarette smokers compared to nonsmokers.

This strong association between smoking and lung cancer is further enhanced by very strong and consistent dose-response relationships. A gradient of increasing risk for lung cancer mortality with increasing numbers of cigarettes smoked per day was established in every one of the prospective studies (Table 4-3). Lung cancer mortality ratios for male smokers who smoked more than 20 cigarettes daily were generally 15 to 25 times greater than those for nonsmokers. Marked increases in lung cancer mortality ratios were also seen in all the lowest dose categories. Males who smoked fewer than 10 cigarettes per day had lung cancer mortality ratios 3 to 10 times

2501031833

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

greater than those for nonsmokers. There is no evidence of a threshold level for the development of smoking-induced lung cancer in any of the studies.

Dose-response relationships with respect to the duration of smoking have also been well established. From the British male physicians study, Peto and Doll (1984) calculated that the excess annual incidence rates of lung cancer after 45, 30, and 15 years of cigarette smoking were in the approximate ratio of 100:20:1 to each other. The California and Swedish studies also demonstrated an increasing risk of lung cancer in men with longer smoking duration (Table 4-4).

Four of the prospective studies examined lung cancer mortality in males by age at initiation of smoking and found increasing risk with younger age (Table 4-5). Some of the studies also investigated smoking cessation in men and observed a decrease in lung cancer risk with increasing number of years since quitting smoking (Table 4-6). The Cancer Prevention Study II, a study of 1,200,000 people in all 50 states, reveals a similar trend for women who quit smoking (Figure 4-3). The occurrence of higher lung cancer mortality ratios in the groups with only a few years since cessation as compared to current smokers (Table 4-6 and Figure 4-3) is attributable to the inclusion of recent ex-smokers who were forced to stop smoking because they already had smoking-related symptoms or illness (U.S. DHHS, 1990). The demonstration of increasing lung cancer risks the younger the age of smoking commencement and decreasing risks with time since smoking cessation establishes the initiation and promotion capabilities of tobacco smoke.

Additional dose-response relationships have been derived from consideration of the types of tobacco products used. Pipe and cigar smokers, who inhale less deeply than cigarette smokers, have lower risks of lung cancer than cigarette smokers (Table 4-7). Furthermore, the American Cancer Society 25-State Study found decreased risks for lung cancer in males and females who smoked cigarettes with lower tar and nicotine content compared to those who smoked cigarettes with higher tar and nicotine content (Table 4-8), although these decreased risks are still substantially higher than the risk to nonsmokers. Similarly, it has been established that smokers of filtered cigarettes have relatively lower lung cancer risks than smokers of nonfiltered cigarettes (Table 4-9). Filters reduce the amount of tars, and hence a portion of the carcinogenic agents, in the MS inhaled by the smoker. Passive smokers, however, do not share in any benefit derived from cigarette filters (see Chapter 3) and may, in fact, be exposed to more ETS if smokers of filtered cigarettes smoke a greater number of cigarettes to compensate for any reduction in nicotine uptake resulting from the filters (U.S. DHHS, 1986).

2501031834

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

4.2.3. Histological Types of Lung Cancer and Associations With Smoking

A number of epidemiologic studies have also examined the association between various histological types of lung cancer and smoking. The results of some of these investigations are summarized in Table 4-10. Problems in interpreting the results of such studies include differences in the nomenclature, criteria, and verification of tumor classification; inadequacy of some specimens, and the small size of many of the patient groups, resulting in unstable risk estimates, particularly in women. There are four major histological types of lung cancer: squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma, and large-cell undifferentiated carcinoma. Sometimes two broad categories--Kreyberg Group I, containing squamous-cell and small-cell carcinomas, and Kreyberg Group II, containing all other epithelial lung cancers, including adenocarcinomas and large-cell undifferentiated carcinomas--are used for classification. The majority of the studies demonstrate an increase in the risk for lung cancer with increasing amount smoked for all four major histological groups in both males and females. The slope of the gradient for adenocarcinomas, however, is shallower than the slopes for the other types.

4.2.4. Proportion of Risk Attributable to Active Smoking

Table 4-11 presents data on the proportion of lung cancer deaths attributable to smoking in various countries. Differences by sex and between countries largely correlate with differences in the proportion of smokers within these populations and the duration and intensity of cigarette usage. In the early 1960s, 50% of U.S. men and 30% of U.S. women smoked, although these proportions have been declining in recent years (Garfinkel and Silverberg, 1991).

In the United States, deaths from lung cancer currently represent one quarter of all cancer deaths. The American Cancer Society predicts there will be 143,000 lung cancer deaths in 1991 (Garfinkel and Silverberg, 1991). Over 85% of this lung cancer mortality is estimated to be attributable to tobacco smoking. In other words, the overwhelming majority of lung cancer deaths, which are a significant portion of all cancer deaths, result from smoking. The strong association between smoking and lung cancer and the dose-response relationships, with effects observable at low doses and no evidence of a threshold, make it highly plausible that passive smoking also causes lung cancer in humans.

4.3. LIFETIME ANIMAL STUDIES

The human evidence for the carcinogenicity of tobacco smoke is corroborated in experimental animal bioassays. The main animal evidence is obtained from inhalation studies in

250103183

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of ETS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments.

Negative responses in short term animal studies (e.g., 60 to 90 days) are not reliable indicators of the carcinogenic potential of a compound because of the long latency period for cancer development. Long-term animal studies at or near the maximum tolerated dose level are used to ensure an adequate power for the detection of carcinogenic activity (U.S. EPA, 1986a).

4.3.1. Inhalation Studies

Although evidence of the carcinogenicity of cigarette smoke originated in humans, attempts were made to develop an inhalation model for smoking in experimental animals in order to study the carcinogenicity of various tobacco products. Such inhalation studies are difficult to conduct, however, because laboratory animals are reluctant to inhale cigarette smoke and will adopt shallow breathing patterns in response to aerosols and irritants. Furthermore, rodents are obligatory nose-breathers, and the anatomy and physiology of the respiratory tract and the biochemistry of the lung differ between rodents and humans. Because of these distinctions, laboratory animals and humans are likely to have different deposition and exposure patterns for the various cigarette smoke components in the respiratory system. For example, rodents have extensive and complex nasal turbinates where significant particle deposition could occur, decreasing exposure to the lung.

The Syrian golden hamster has been the most useful animal inhalation model found so far for studying smoking-induced carcinogenesis. It is more tolerant of tobacco smoke than mice and rats and is relatively resistant to respiratory infections. The hamster also has a low background incidence of spontaneous pulmonary tumors and is, in fact, refractory to the induction of lung cancers by known carcinogenic agents. The inhalation of tobacco smoke by the hamster does, however, induce carcinomas of the larynx. In one study (Dontenwill et al., 1973), three groups of 80 male and 80 female Syrian golden hamsters were exposed for 10 minutes to air-diluted cigarette smoke (1:15) once, twice, or three times daily, 5 days per week, for their lifetimes. Pre-invasive carcinomas of the upper larynx were detected in 11.3%, 30%, and 30.6% of the animals, respectively, and invasive carcinomas were found in 0.6%, 10.6%, and 6.9%, respectively. No laryngeal tumors were observed in control animals. In another experiment, exposure for 59 to 80 weeks to a 11% or 22% cigarette smoke aerosol twice daily for 12 minutes resulted in laryngeal carcinomas in 3 of 44 and 27 of 57 animals, respectively, providing some evidence of a dose-

25010318 36

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

response relationship for the induction of carcinoma of the larynx by cigarette smoke (Bernfeld et al., 1979). Bernfeld et al. suggest that the greater deposition of tar per unit of surface area in the larynx compared to the lung may explain the high yield of laryngeal cancers and lack of lung tumors in this animal model.

4.3.2. Intrapulmonary Implantations of Cigarette Smoke Condensates

Because of the difficulties with inhalation studies of cigarette smoke, some in vivo studies examine the carcinogenicity of cigarette smoke condensate (CSC) collected from smoking machines. CSC assays may not, however, reveal all of the carcinogenic activity of actual cigarette smoke, since these condensates lack most of the volatile and semivolatile components of whole smoke. In lifetime rat studies, intrapulmonary implants of CSC in a lipid vehicle cause a dose-dependent increase in the incidence of lung carcinomas (Stanton et al., 1972; Dagle et al., 1978).

ETS condensates have also demonstrated carcinogenicity when implanted into rat lungs (Grimmer et al., 1988). (Actually, only sidestream smoke was examined, but this constitutes roughly 85% of ETS [Fielding, 1985].) Sidestream smoke (SS) emitted by a smoking machine was separated into condensate fractions containing the semivolatiles, the polycyclic aromatic hydrocarbon (PAH)-free particulates and the PAHs with two or three rings, or the PAHs with four or more rings. These fractions were implanted into female Osborne-Mendel rats, following the procedure of Stanton et al. (1972), at a dose level of one cigarette per animal. At the end of the lifetime study, none of the 35 rats in each of the untreated control, vehicle control, or semivolatile-exposed groups had lung carcinomas. In the group exposed to the fraction containing PAH-free particulates and PAHs with two or three rings, there was 1 lung carcinoma in 35 animals. In the group exposed to the fraction comprising PAHs with four or more rings, there were 5 lung carcinomas in 35 rats. An additional group that was exposed to a dose of 0.03 mg benzo[a]pyrene (BaP) per rat exhibited 3 lung carcinomas in 35 animals. The condensate fraction containing BaP and the other PAHs with four or more rings from the SS generated by a single cigarette contains about 100 ng of BaP. Assuming a linear, nonsynergistic dose-response relationship, this would suggest that less than 1% of the total carcinogenicity of that CSC fraction can be attributed to the BaP present in the smoke.

4.3.3. Mouse Skin Painting of Cigarette Smoke Condensates

In addition, numerous studies have shown that when CSC suspended in acetone is chronically applied to mouse skin, significant numbers of the mice develop papillomas or

2501031837

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

carcinomas at the site of application (e.g., Wynder et al., 1957; Davies and Day, 1969). Mouse skin studies have also demonstrated that CSC has both tumor-initiating and tumor-promoting capabilities (Hoffman and Wynder, 1971).

One mouse skin painting study examined the carcinogenicity of ETS condensate (Wynder and Hoffman, 1967). Cigarette tar from SS deposited on the funnel of a smoking machine was suspended in acetone and administered to mouse skin. Fourteen of thirty mice developed skin papillomas, and 3 of 30 developed carcinomas. In a parallel assay in the same study, a suspension of MS condensate applied to deliver a comparable amount of condensate to the skin of 100 mice yielded benign skin tumors in 24 and malignant tumors in 6 of the mice. This suggests that the condensate of SS has greater mouse skin tumorigenicity per unit weight than that of MS.

4.4. GENOTOXICITY

Supportive evidence for the carcinogenicity of tobacco smoke is provided by the demonstration of genotoxicity in numerous short-term assays. Extensive reviews of these studies can be found in IARC (1986) and DeMarini (1983), and only the highlights are presented here. A few studies deal with whole smoke, but most examine CSC. Tobacco smoke is genotoxic in virtually every in vitro system tested, providing overwhelming supportive evidence for its carcinogenic potential.

In *Salmonella typhimurium*, for example, Basrur et al. (1978) found that whole smoke and smoke condensates from various types of tobacco were mutagenic in the presence of a metabolic activating system. SS (Ong et al., 1984) and extracts of ETS collected from indoor air (Lofroth et al., 1983; Alfeim and Randahl, 1984; Lewtas et al., 1987; Ling et al., 1987; Lofroth et al., 1988) also exhibit mutagenic activity in this bacterium. Claxton et al. (1989) found that SS accounted for approximately 60% of the total *S. typhimurium* mutagenicity per cigarette--40% from the ETS particulates and 20% from the ETS semivolatiles. The highly volatile fraction, from either MS or SS, was not mutagenic.

Similarly, cigarette smoke produced mitotic gene conversion, reverse mutation, and reciprocal mitotic recombination in fungi (Gairola, 1982). In addition, CSCs induce mutations, sister chromatid exchanges, and cell transformation in various mammalian cells in culture. Putnam et al. (1985) demonstrated dose-dependent increases in sister chromatid exchange frequencies in bone-marrow cells of mice exposed to cigarette smoke for 2 weeks.

2501031838

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

4.5. SUMMARY AND CONCLUSIONS

The unequivocal causal association between tobacco smoking and lung cancer in humans with dose-response relationships extending down to the lowest observed exposures, as well as the corroborative evidence of the carcinogenicity of both MS and ETS provided by animal bioassays and in vitro studies, clearly establish the plausibility that ETS is also a human lung carcinogen. Furthermore, biomarker studies verify that passive smoking results in detectable uptake of tobacco smoke constituents by nonsmokers, affirming that ETS exposure is a public health concern (Chapter 3).

Active smoking induces squamous-cell carcinomas, small-cell carcinomas, large-cell carcinomas, and adenocarcinomas in humans, all in a dose-related manner. Lung cancer mortality rates have increased dramatically over the past 60 years in males and, more recently, in females, with increasing cigarette consumption. High relative risks for lung cancer, associated with the number of cigarettes smoked per day, have been demonstrated in countless studies, with no evidence of a threshold level of exposure. Dose-response relationships have also been established with respect to duration of smoking. Lung cancer risk increases the younger the age at initiation of smoking and decreases the longer the time since cessation of smoking. These latter trends, coupled with the evidence from mouse skin painting studies, show that tobacco smoke has both tumor-initiating and tumor-promoting capabilities.

Inhalation studies in hamsters confirm that tobacco smoke is carcinogenic to the respiratory tract. In addition, mouse skin painting experiments and intrapulmonary implantations in rats have demonstrated the carcinogenicity of condensates from both MS and ETS. Numerous genotoxicity tests contribute supporting evidence for the carcinogenic potential of cigarette smoke and smoke condensates. The mutagenicity of ETS and its extracts has also been established. As discussed in Chapter 3, MS and ETS are qualitatively similar in composition, and both contain a number of known and suspected human carcinogens.

In fact, these observations alone--the dose-related association between tobacco smoking and lung cancer in humans, which extends to the lowest reported doses; the chemical similarity between MS and ETS; and the confirmation of the carcinogenicity of MS and ETS in animal and in vitro experiments--are sufficient to establish weight-of-evidence for the carcinogenicity of ETS to humans. According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the

25010318 39

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

agents and cancer." The *Guidelines* establish "three criteria (that) must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

Given the strong dose-related associations with high relative risks consistently observed across numerous independent studies from several countries and the biological plausibility provided by ancillary evidence of the genotoxicity and animal carcinogenicity of MS and by knowledge of the existence of specific carcinogenic components within MS, confounding, bias, and chance can all be ruled out as possible explanations for the observed association between active smoking and lung cancer. Therefore, under the EPA carcinogen classification system, MS would be a Group A (known human) carcinogen, and, due to the similarity in chemical composition between MS and ETS and the known human exposure to ETS (Chapter 3), ETS would also be classified as a known human carcinogen.

In addition, however, there exists a whole body of evidence dealing specifically with human exposure to ETS. Substantial epidemiologic evidence demonstrates increased risks of lung cancer in nonsmokers exposed to actual ambient levels of ETS. Therefore, unlike with many environmental hazards where extrapolation from high-dose animal bioassays or high-level, generally occupational, human exposures must be used to estimate the human risk at environmental levels of exposure, the health risk of ETS exposure can be examined directly from the epidemiologic data. The epidemiologic evidence for the human lung carcinogenicity associated specifically with ETS is the subject of Chapter 5.

250103184O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-1. Main characteristics of major cohort studies on the relationship between smoking and cancer

Study	Year of enrollment	Sample size; initial samples; in brackets, population for follow-up	Source of information on smoking (proportion of respondents)	Duration of follow-up and no. of deaths	Completeness of follow-up for mortality
ACS Nine-state study	1952	204,547 men [187,783]	Self-administered questionnaire	44 months 11,870 deaths	98.9%
Canadian veterans study	1955-1956	207,397 subjects (aged 30+) [92,000]	Self-administered questionnaire (57% respondents)	6 years 9,491 deaths in men; 1,794 deaths in women	NA
British doctors study	1951	34,440 men (aged 20+)	Self-administered questionnaire (69% respondents)	20 years 10,072 deaths	99.7%
		6,194 women (aged 20+)	Self-administered questionnaire (60% respondents)	22 years 1,094 deaths	99%
ACS 25-state study *	1959-1960	1,078,894 subjects First follow-up: 440,558 men, 562,671 women (aged 35-84); second follow-up: 358,422 men, 483,519 women	Self-administered questionnaire	4.5 + 5 years 26,448 deaths in men; 16,773 deaths in women	97.4% in women 97.9% in men in first follow-up
U.S. veterans study	1954	293,958 men (aged 31-84) [248,046]	Self-administered questionnaire (85% respondents)	16 years 107,563 deaths	Almost 100% ascertainment of vital status; 97.6% of death certificates retrieved

(continued on the following page)

2501031841

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-1. (continued)

Study	Year of enrollment	Sample size; initial samples; in brackets, population for follow-up	Source of information on smoking (proportion of respondents)	Duration of follow-up and no. of deaths	Completeness of follow-up for mortality
Californian study	1954-1957	68,153 men (aged 35-64)	Self-administered questionnaire	5-8 years 4,706 deaths	NA
Swedish study	1963	27,342 men, 27,732 women (aged 18-69)	Self-administered questionnaire (89% respondents)	10 years 5,655 deaths (2,968 autopsies)	NA
Japanese study	1965	122,261 men, 142,857 women (aged 40+)	Interview (95% of population in area)	16 years 51,422 deaths	Total

NA = not available.

Source: IARC, 1986.

25010318 42

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-2. Lung cancer mortality ratios--prospective studies

Population	Size	Number of Deaths	Nonsmokers	Cigarette Smokers
British doctors study	34,000 males 6,194 females	441 27	1.00 1.00	14.0 5.0
Swedish study	27,000 males 28,000 females	55 8	1.00 1.00	7.0 4.5
Japanese study	122,000 males 143,000 females	940 304	1.00 1.00	3.76 2.03
ACS 25-State study	358,000 males 483,000 females	2,018 439	1.00 1.00	8.53 3.58
U.S. veterans	290,000 males	3,126	1.00	11.28
Canadian veterans	78,000 males	331	1.00	14.2
ACS 9-state study	188,000 males	448	1.00	10.73
California males in 9 occupations	68,000 males	368	1.00	7.61

Source: U.S. DHHS, 1982.

2501031843

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-3. Lung cancer mortality ratios for men and women, by current number of cigarettes smoked per day--prospective studies

Population	Men		Women	
	Cigarettes smoked per Day	Mortality ratios	Cigarettes smoked per day	Mortality ratios
ACS 25-state study	Nonsmoker	1.00	Nonsmoker	1.00
	1-9	4.62	1-9	1.30
	10-19	8.62	10-19	2.40
	20-39	14.69	20-39	4.90
	40+	18.71	40+	7.50
British doctors study	Nonsmoker	1.00	Nonsmoker	1.00
	1-14	7.80	1-14	1.28
	15-24	12.70	15-24	6.41
	25+	25.10	25+	29.71
Swedish study	Nonsmoker	1.00	Nonsmoker	1.00
	1-7	2.30	1-7	1.80
	8-15	8.80	8-15	11.30
	16+	13.70	16+	--
Japanese study (all ages)	Nonsmoker	1.00	Nonsmoker	1.00
	1-19	3.49	< 20	1.90
	20-39	5.69	20-29	4.20
	40+	6.45		
U.S. veterans study	Nonsmoker	1.00		
	1-9	3.89		
	10-20	9.63		
	21-39	16.70		
	≥ 40	23.70		
ACS 9-state study	Nonsmoker	1.00		
	1-9	8.00		
	10-20	10.50		
	20+	23.40		
Canadian veterans	Nonsmoker	1.00		
	1-9	9.50		
	10-20	15.80		
	20+	17.30		
California males in nine occupations	Nonsmoker	1.00		
	about ½ pk	3.72		
	about 1 pk	9.05		
	about 1½ pk	9.56		

Source: U.S. DHHS, 1982.

2501031844

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-4. Relationship between risk of lung cancer and duration of smoking in men, based on available information from cohort studies

Reference	Duration of smoking (years)	Standardized mortality ratio (no. of observed deaths)	Approximate annual excess death rate (%)
Weir & Dunn (1970)	1-9	1.13	0.002 (0.001)
	10-19	6.45	0.09 (0.05)
	20+	8.66	0.12 (0.08)
	nonsmokers	1.0	0
Cederlöf et al. (1975)	1-29	1.8 (5)	0.01 (0.008)
	>30	7.4 (23)	0.1 (0.06)
	nonsmokers	1.0 (7)	0

The mortality ratio among nonsmokers was assumed to be 15.6/100,000 per year, as in the American Cancer Society 25-state study. Figures in parentheses were computed by the IARC working group, applying the British doctors' mortality rate among nonsmokers (10.0/100,000 per year).

Source: IARC, 1986.

25010318H5

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-5. Lung cancer mortality ratios for males, by age of smoking initiation--prospective studies

Study	Age of smoking initiation in years	Mortality ratio
ACS 25-state study	Nonsmoker	1.00
	25+	4.08
	20-24	10.08
	15-19	19.69
	Under 15	16.77
Japanese study	Nonsmoker	1.00
	25+	2.87
	20-24	3.85
	Under 20	4.44
U.S. veterans	Nonsmoker	1.00
	25+	5.20
	20-24	9.50
	15-19	14.40
	Under 15	18.70
Swedish study	Nonsmoker	1.00
	19+	6.50
	17-18	9.80
	Under 16	6.40

Source: U.S. DHHS, 1982

2501031846

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-6. Relationship between risk of lung cancer and number of years since stopping smoking, in men, based on available information from cohort studies

Reference	No. of years since stopping smoking	Mortality ratio (no. of observed deaths)
ACS 25-state study (Hammond, 1966)	1-19 cig./day	
	Current smokers	6.5 (80)
	<1	7.2 (3)
	1-4	4.6 (5)
	5-9	1.0 (1)
	10+	0.4 (1)
	Nonsmokers	1.0 (32)
	20+ cig./day	
	Current smokers	13.7 (351)
	<1	19.1 (33)
	1-4	12.0 (33)
	5-9	7.2 (32)
	10+	1.1 (5)
	Nonsmokers	1.0 (32)
Swedish study (Cederlöf et al., 1975)	<10	6.1 (12)
	>10	1.1 (3)
	Nonsmokers	1.0 (7)
British doctors study (Doll & Peto, 1976)	Current smokers	15.8 (123)
	1-4	16.0 (15)
	5-9	5.9 (12)
	10-14	5.3 (9)
	15+	2.0 (7)
	Nonsmokers	1.0 (7)
Rogot & Murray (1980)	Current smokers	11.3 (2609)
	<5	18.8 (47)
	5-9	~7.5 (86)
	10-14	~5.0 (100)
	15-19	~5.0 (115)
	20+	2.1 (123)
	Nonsmokers	1.0 NA

NA = not available.

Source: IARC, 1986.

2501031847

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-7. Relative risks of lung cancer in some large cohort studies among men smoking cigarettes and other types of tobacco

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
ACS Nine-state study[1]	Never smoked	1.0	12.8	15
	Occasionally only	1.5	19.2	8
	Cigarettes only	9.9	27.2	249
	Cigars only	1.0	13.1	7
	Pipes only	3.0	38.5	18
	Cigarettes + other	7.6	97.7	148
	Cigars + pipes	0.6	7.3	3
Canadian veterans study	Nonsmokers	1.0		7
	Cigarettes only	14.9		325
	Cigars only	2.9		2
	Pipe only	4.4		18
	Ex-smokers	6.1		18
ACS 25-state study[1]	Never smoked	1.0	12	49
	Cigarettes only	9.2	111	719
	Cigars only	1.9	22	23
	Pipes only	2.2	27	21
	Cigarettes + other	7.4	89	336
	Cigars + pipes	0.9	11	11
Swedish study[1]	Nonsmokers	1.0		7
	Cigarettes only	7.0		28
	Cigarettes + pipe	10.9		27
	Pipe only	7.1		31
	Cigars only	9.2		6
	Ex-smokers	6.1		12

(continued on the following page)

2501031848

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-7. (continued)

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
British doctors study	Nonsmokers	1.0	10	
	Current smokers	10.4	104	
	Cigarettes only	14.0	140	
	Pipes and/or cigars only	5.8	58	
	Cigarettes + other	8.2	82	
	Ex-smokers	4.3	43	
U.S. veterans study[1]	Nonsmokers	1.0		2609
	Cigarettes	11.3		1095
	Cigarettes only	12.1		41
	Cigars only	1.7		32
	Pipes only	2.1		517
	Ex-cigarette smokers	4.0		
Norwegian study[1]	Nonsmokers	1.0		7
	Cigarettes	9.7		88
	Cigarettes only	9.5		70
	Pipes or cigars only	2.6		12
	Ex-smokers	2.8		11

[1]Figures given in original report.

Source: IARC, 1986.

250103189

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-8. Age-adjusted lung cancer mortality ratios for males and females, by tar and nicotine (T/N) in cigarettes smoked

	Males	Females
High T/N[1]	1.00	1.00
Medium T/N	0.95	0.79
Low T/N	0.81	0.60

[1]The mortality rate for the category with highest risk was made 1.00 so that the relative reductions in risk with the use of lower T/N cigarettes could be visualized.

Source: U.S. DHHS, 1982.

2501031850

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-9. Relative risk for lung cancer by type of cigarette smoked (filter vs. nonfilter), in men, based on cohort and case-control studies

Reference	Type of study	Relative risk
Hawthorne & Fry (1978)	Cohort	0.8
Rimington (1981)	Cohort	0.7
Bross & Gibson (1968)	Case-control	0.6
Wynder et al. (1970)	Case-control	0.6
Dean et al. (1977)	Case-control	0.5

Source: IARC, 1986.

250103185

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-10. Main results of studies dealing with the relationship between smoking and different histological types of lung cancer

Reference	Histological type	Results						Comments
Doll et al. (1957)		Sex	No. of Cases	Relative Risk				Nonsmokers, 1.0 (RR) No. observed
				Amount of Tobacco Smoked (g)				
				<5	5-14	15-24	25+	
	Kreyberg I	M	829	4.7	10.6	14.3	25.4	3
		F	32	1.0	1.7	8.3		16
	Kreyberg II	M	38	0.5	0.8	1.2	1.1	2
		F	8	1.1	2.3	4.1		5
Hammond & Horn (1958b)		Relative risk no. of packs/day						Nonsmokers, 1.0 Only regular smokers considered
		<½		½-1		1+		
	Adenocarcinoma	2.0		2.5		7.0		
	Other types	16.3		25.5		88.0		
Doll & Hill (1964a)		Death Rate/1000 Amount of tobacco smoked						Men only
		Ex-Smokers		1-14g	15-24g	25+g		
	Squamous-cell carcinoma	0.09		0.22	0.33	0.45		
	Small-cell and anaplastic carcinoma	0.05		0.10	0.20	0.38		
	Adenocarcinoma	0.03		0.03	0.12	0.07		

(continued on the following page)

DRAFT--DO NOT QUOTE OR CITE

250103185Z

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-10. (continued)

Reference	Histological Type	Results					Comments
Haenszel & Taeuber (1964)		Standardized mortality ratio					Women only; standardized mortality ratio; total group, 1.00
		Never smoked	Ex-smokers	Occasional cigarette Smokers	Regular cigarette smokers <1 pack/day	Regular cigarette smokers >1 pack/day	
	Adenocarcinoma	0.78	0.35	2.46	1.17	7.50	
	Squamous-cell and undifferentiated carcinoma	0.59	0.52	1.15	2.19	8.78	
Hanbury (1964)		No. of cases (%)					Women only
		"Heavy" and "medium" smokers		Nonsmokers and "Remainder"			
	Small-cell carcinoma	18 (47)		21 (34)			
	Undifferentiated carcinoma	9 (24)		14 (23)			
	Squamous-cell carcinoma	9 (24)		12 (19)			
	Adenocarcinoma	2 (5)		15 (24)			

Vincent, T.N. et al. (1965)		Total no. of cases	Number of cigarettes smoked/day										Women only
			None		1-20		21-40		41+		Unknown		
			No.	%	No.	%	No.	%	No.	%	No.	%	
	Squamous-cell	19	10	53	3	16	2	10	2	10	2	10	
	carcinoma	17	2	12	7	41	6	35	2	12	0	0	
	Small-cell carcinoma	64	51	80	6	9	4	6	0	0	3	5	
	Adenocarcinoma	22	12	54	4	18	6	27	0	0	0	0	
	Undifferentiated	41	32	78	8	20	1	2	0	0	0	0	
	Others	163	107	66	28	17	19	12	4	2	5	3	

DRAFT--DO NOT QUOTE OR CITE

05/15/92

2501031853

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-10. (continued)

Reference	Histological Type	Results			Comments
Deaner & Trummer (1979)		Pack-years	Number of Tumors	Smokers	
	Undifferentiated carcinoma	40	40	40 (100%)	
	Adenocarcinoma	12	19	13 (68%)	
	Squamous-cell carcinoma	52	9	9 (100%)	
Wynder et al. (1970)		Sex	No.(%)		Heavy = 41+ cigarettes/day
			Cigarette Smokers	Heavy Smokers	
	Kreyberg I	M	191 (91.0)	59 (29.9)	
		F	24 (80.0)	3 (12.0)	
	Kreyberg II	M	61 (82.4)	9 (14.1)	
		F	21 (58.3)	1 (4.8)	
	Controls	M	199 (47.4)	26 (9.8)	
		F	53 (40.2)	3 (5.4)	
Weiss, W. et al. (1972)		Death rate per 1,000 man-years of observation (adjusted for age and race) No. of cigarettes/day			
		1-10	10-19	20+	
	Squamous-cell carcinoma	-	0.8	2.1	
	Well differentiated	0.7	0.4	1.0	
	Poorly differentiated	-	0.3	0.7	
	Small-cell carcinoma	-	0.6	1.0	
	Adenocarcinoma				

DRAFT--DO NOT QUOTE OR CITE

05/15/92 2501031854

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-10. (continued)

Reference	Histological Type	Result	Comments
Vincent, R.G. et al. (1977)		No. of Cigarettes Smoked/Day 0 / 1-20 / 21-40 / 41+ / Other	
	Squamous-cell carcinoma	14 / 219 / 110 / 120 / 16	
	Adenocarcinoma	28 / 101 / 66 / 53 / 7	
	Small-cell carcinoma	4 / 103 / 62 / 56 / 6	
	Large-cell carcinoma	2 / 40 / 32 / 33 / 0	
	Bronchiolo-alveolar carcinoma	6 / 20 / 9 / 6 / 0	
	Mixed	0 / 9 / 5 / 5 / 0	
	Other	6 / 30 / 19 / 17 / 4	
Chan et al. (1979)		Smoking Category (kg Tobacco Smoked During Lifetime) Non-smokers / ≤100: Manufactured / ≤100: All / 100-199: Manufactured / 100-199: All / ≥200: Manufactured / ≥200: All	Women only
	Squamous-cell and small-cell carcinomas	1.0 / 3.6 / 3.4 / 3.7 / 4.2 / 2.6 / 4.1	
	Adenocarcinoma	1.0 / 1.9 / 1.4 / 1.4 / 1.8 / 1.6 / 1.7	

DRAFT--DO NOT QUOTE OR CITE

2501031855

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-10. (continued)

Joly, O.G. et al. (1983)	Relative Risk by Duration of Smoking (Years)								Nonsmokers, 1.0
	Men				Women				
	1-29	30-39	40-49	50+	1-29	30-39	40-49	50+	
Squamous-cell carcinoma	15.0	15.9	39.5	42.2	4.4	9.4	31.4	51.9	
Adenocarcinoma	2.0	3.2	5.3	5.7	2.1	2.7	4.7	4.0	
Undifferentiated carcinoma	26.0	26.4	40.7	50.0	3.9	15.6	20.6	28.3	
Poorly differentiated carcinoma	6.4	7.7	10.8	10.2	3.2	7.8	5.6	13.1	

Source: IARC, 1986.

DRAFT--DO NOT QUOTE OR CITE

250103185 6

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 4-11. Lung cancer death attributable to tobacco smoking in certain countries

Country	Year	No. of Deaths[1]	Expected Deaths in Nonsmokers[2]	Crude Rate in Persons Aged 35+ Observed	Crude Rate in Persons Aged 35+ In Non-Smokers	AC[3]	AP[4]
Canada							
Men	1978	6,435	556	142.8	11.8	5,762	0.9
Women	1978	1,681	487	34.0	9.9	1,194	0.71
England & Wales							
Men	1981	26,297	1,576	228.5	13.3	24,720	0.94
Women	1981	8,430	1,663	63.3	12.4	6,767	0.80
Japan							
Men	1981	16,638	2,868	64.8	10.7	13,184	0.83
Women	1981	6,161	2,593	21.0	8.9	3,568	0.58
Sweden							
Men	1981	1,777	301	85.0	14.0	1,476	0.83
Women	1981	654	281	28.0	12.3	373	0.57
USA							
Men	1979	72,803	5,778	166.7	12.7	67,024	0.92
Women	1979	25,648	5,736	50.0	11.1	19,912	0.78

[1]From the Global Epidemiological Surveillance and Health Situation Assessment data bank of WHO.
[2]Calculated by IARC, 1986. Slightly overestimates number of expected deaths.
[3]AC, number of cases attributable to smoking.
[4]AP, proportion of cases attributable to smoking.

Source: IARC, 1986.

250103185?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

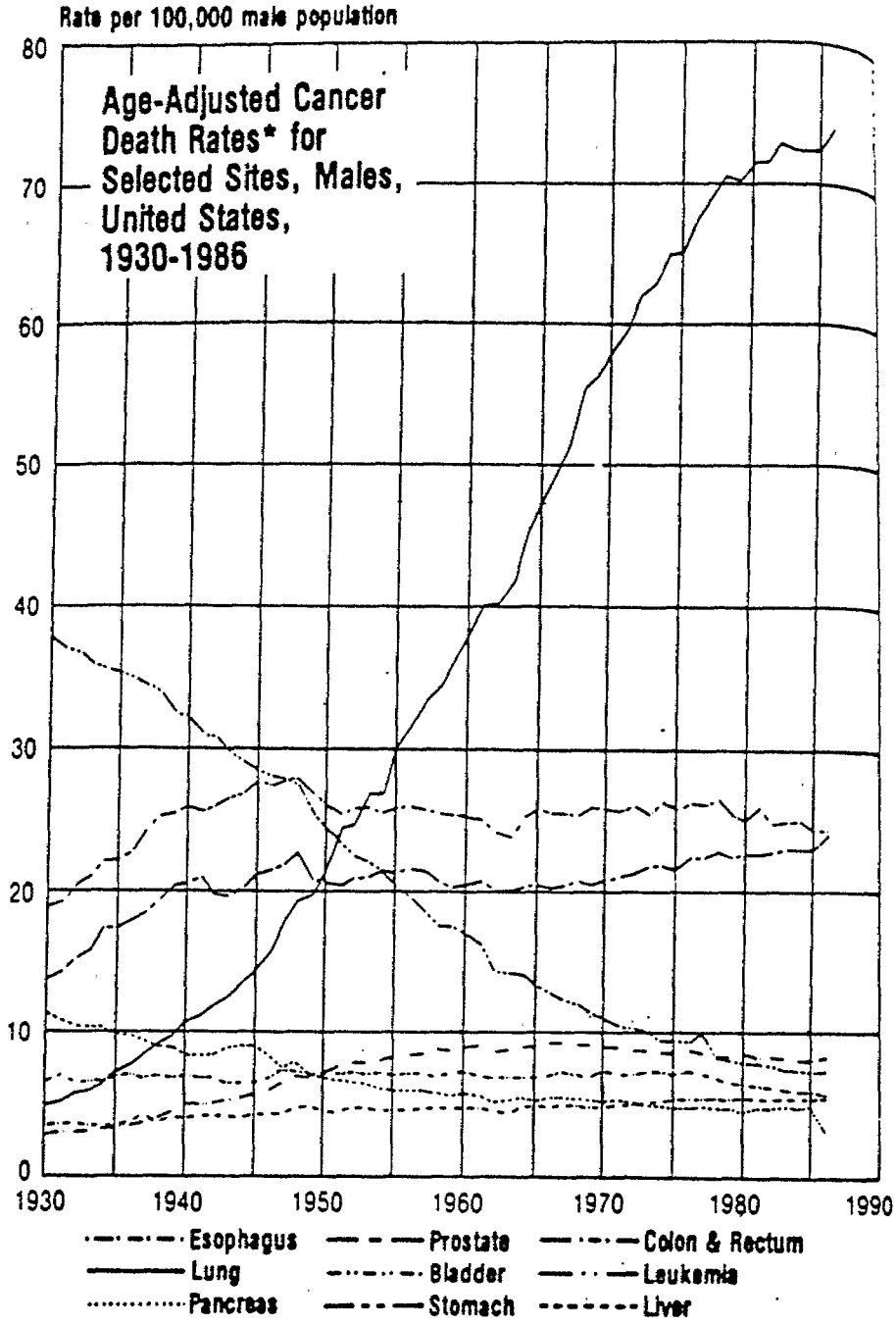


Figure 4-1. Age-adjusted cancer death rates* for selected sites, males, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

250103185B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

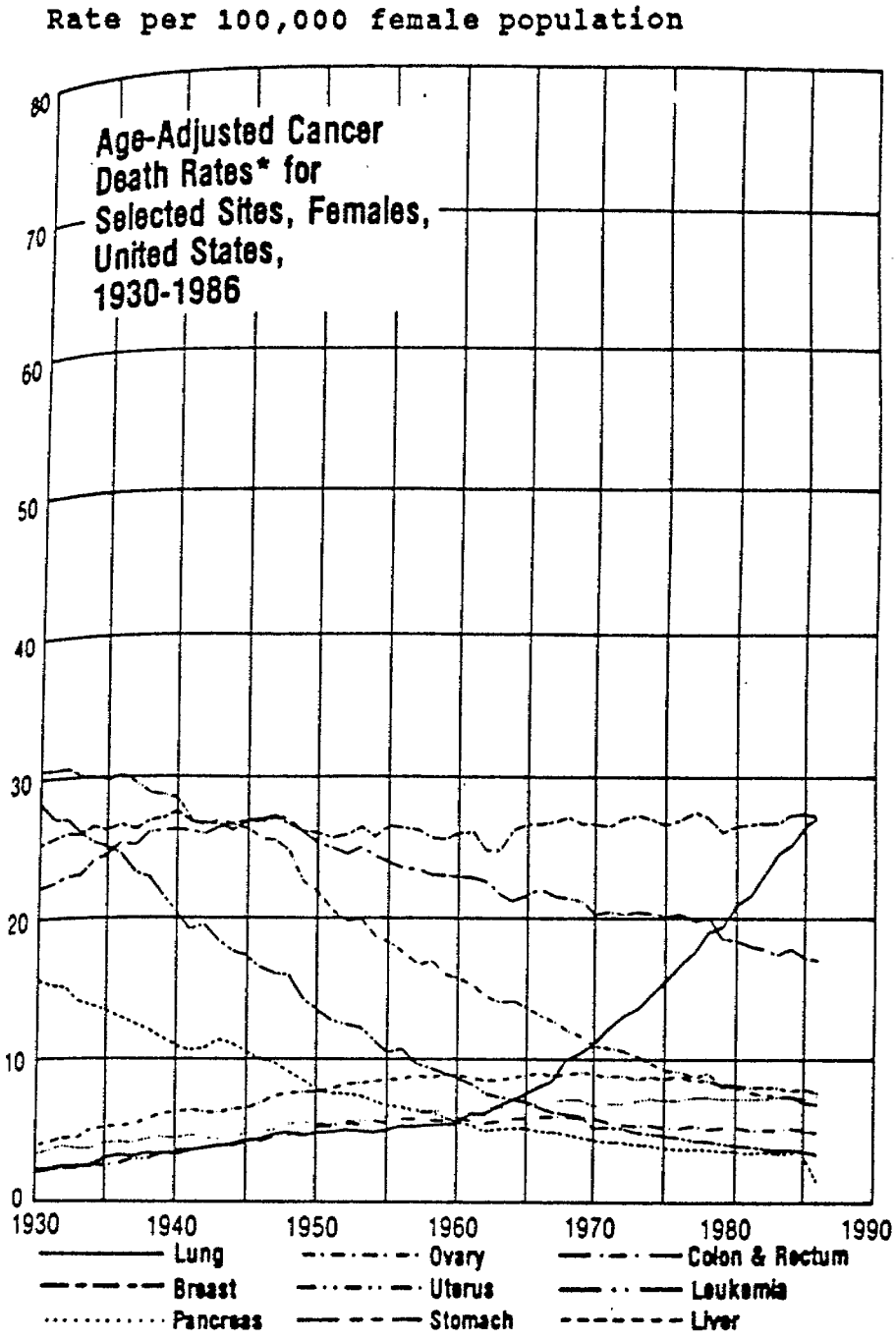


Figure 4-2. Age-adjusted cancer death rates* for selected sites, females, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

2501031859

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

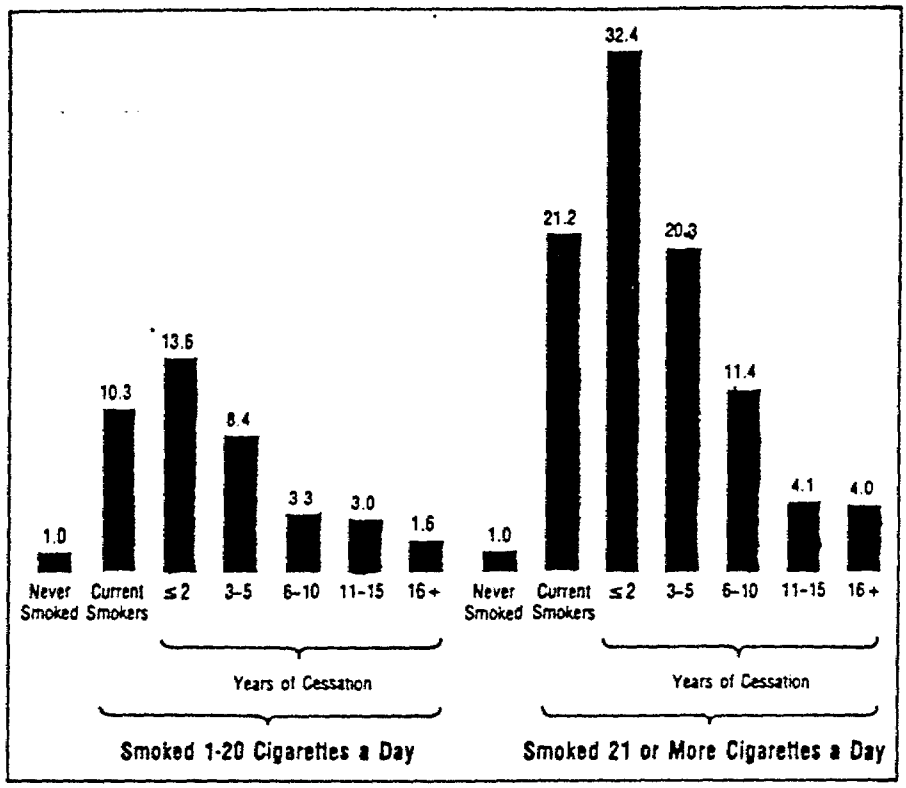


Figure 4-3. Relative risk of lung cancer in ex-smokers, by number of years quit, women, Cancer Prevention Study II

Source: Garfinkel and Silverberg, 1991.

2501031860

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

5. HAZARD IDENTIFICATION II: INTERPRETATION OF EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

5.1. INTRODUCTION

The Centers for Disease Control attributed 434,000 U.S. deaths in 1988 to smoking (CDC, 1991a). Major disease groups related to smoking mortality include lung cancer, chronic obstructive pulmonary disease, coronary heart disease, and stroke, with smoking accountable for an estimated 87%, 82%, 21%, and 18% of total deaths, respectively. Lung cancer alone accounted for about 25% to 30% of the total smoking mortality with some 100,000 deaths. The age-standardized annual lung cancer mortality rates for 1985 are estimated at 12 per 100,000 for females and 15 per 100,000 for males who never smoked but 130 per 100,000 for female and 268 for male cigarette smokers, a relative risk of 10.8 and 17.4, respectively (Garfinkel and Silverberg, 1991).

Chapter 4 discusses the biological plausibility that passive smoking may also be a risk factor for lung cancer because of the qualitative similarity of the chemical constituency of sidestream smoke, the principal source of environmental tobacco smoke (ETS), and mainstream smoke taken in during the act of "puffing" on a cigarette, and because of the apparent non-threshold nature of the dose-response relationship observed between active smoking and lung cancer. Although the relative risk of lung cancer from passive smoking would undoubtedly be much smaller than that for active smoking, the ubiquity of ETS exposure (Chapter 3) makes potential health risks worth investigating. This chapter analyzes the data from the large number of epidemiologic studies on ETS and lung cancer. There is sufficient empirical evidence derived from human experience under real-life conditions to assess the lung cancer hazard of ETS without the attendant uncertainties of extrapolation of risk across species (e.g., from controlled animal experiments, or from high dose to low dose, as required from human data obtained from atypically high exposure levels). Virtually all of the 31 studies available classify never-smoking women as "exposed" or "unexposed" to ETS based on self- or proxy-reported smoking in the subject's environment, usually according to whether or not a woman is married to a smoker. Consequently, the data are best suited for estimation of the relative risk of lung cancer mortality between the exposed and unexposed groups and determination of whether a difference in lung cancer risk between the classifications is sufficiently large to be detectable with epidemiologic data. The use of a dose-surrogate such as spousal smoking and dichotomization of persons as

250103186

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

exposed or unexposed is not as well suited for characterization of population risk, although estimates can be constructed.

Epidemiologic evidence of an association between passive smoking and lung cancer first appeared 10 years ago in a prospective cohort study in Japan (Hirayama, 1981a) and a case-control study in Greece (Trichopoulos et al., 1983). Both studies concluded that the lung cancer incidence and mortality in nonsmoking women was higher for women married to smokers than for those married to nonsmokers. Although there are other sources of exposure to ETS, particularly outside the home, the assumption is that women married to smokers are exposed to more tobacco smoke, on average, than women married to nonsmokers. These two studies, particularly the cohort study from Japan, evoked considerable critical response. They also aroused the interest of public health epidemiologists, who initiated additional studies.

At the request of two Federal agencies--the U.S. Environmental Protection Agency (Office of Air and Radiation) and the Department of Health and Human Services (Office of Smoking and Health)--the National Research Council (NRC) formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on the health consequences. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail and includes summary analyses of the evidence from 10 case-control and 3 cohort (prospective) studies. It concludes, "Considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers."

The NRC committee was particularly concerned about the potential bias in the study results caused by the fact that current and former smokers may have incorrectly self-reported as lifelong nonsmokers (never-smokers). Using reasonable assumptions for misreported smoking habits, the committee determined that a plausible range for the true relative risk is 1.15 to 1.35, with 1.25 the most likely value. When these relative risks are also corrected for background exposure to ETS to make the risk relative to a baseline of zero ETS exposure, the resultant estimate is 1.42, with a plausible range of 1.24 to 1.61.

Two other major reports on passive smoking have appeared: the Surgeon General's report on the health consequences of passive smoking (U.S. DHHS, 1986) and the report on methods of analysis and exposure measurement related to passive smoking by the International Agency for Research on Cancer (IARC, 1987). The Surgeon General's report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with

2501031862

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

exposures to ETS lead to the conclusion that involuntary smoking is a cause of lung cancer.

The IARC committee emphasized issues related to the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. Included in the 1987 IARC report is a citation from the summary statement on passive smoking of a previous IARC report that the epidemiologic evidence available at that time (1985) was compatible with either the presence or absence of lung cancer risk. Based on other considerations related to biological plausibility, however, it concludes that passive smoking gives rise to some risk of cancer. Specifically, the report (IARC, 1986) states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive smoking," and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens . . . leads to the conclusion that passive smoking gives rise to some risk of cancer.

In the 5 years since those reports, the number of studies available for analysis has more than doubled. There are now 31 epidemiologic studies available from eight different countries, listed in Table 5-1. Twenty-seven employ case-control designs, denoted by the first four letters of the first author's name for convenient reference, and four are prospective cohort studies, distinguished by the designation "(Coh)." Six case-control studies, FONT (USA), JANE (USA), KALA (Greece), LIU (China), SOBU (Japan), and WUWI (China), have been published as recently as 1990. The small cohort study from Scotland (Gillis et al., 1984) has been updated and is now included under the name HOLE(Coh); another small cohort study on Seventh-Day Adventists in the United States, an unpublished dissertation, is included as BUTL(Coh). The abstracts for a second case-control study by Kabat and Wynder and a new one by Stockwell and colleagues are included in the critical analysis in Appendix A, but insufficient information is available to include their results.

Because of coincidental timing, the 1986 reports of the Surgeon General and the NRC review approximately the same epidemiologic studies available for review. More specifically, the NRC report includes 10 of the studies shown in Table 5-1: AKIB, CHAN, CORR, GARF, KABA, KOO, LEE, PERS, and TRIC; WU was available but not included because the crude data were not reported. (Crude data consist of the number of exposed and unexposed subjects among lung cancer cases and controls, where a subject is typically classified as exposed to ETS if married to a smoker.) The NRC also excluded an earlier version of the KOO study and the studies by Knoth et al. (1983) (no reference population was given), Miller (1984) (did not report on lung cancers separately), and Sandler et al. (1985) (included very few lung cancers). Aside from WU, these studies are also omitted from this report for the same reasons.

2501031863

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The subscripts on study names in Table 5-1 refer to the "tier" number assigned to it. Following the statistical analysis of all studies (Sections 5.2 and 5.3), each study is examined individually for sources of bias and confounding that might affect validity of its results for assessing ETS and lung cancer, and it is given a tier number from 1 to 4 accordingly (Sections 5.4.2 to 5.4.4). Pooled estimates of relative risk by country are then recalculated by tiers, beginning with the studies considered most valid (Tier 1) and adding Tiers 2, 3, and 4 successively (Section 5.4.5) to see how sensitive the outcome is to the choice of studies selected in this manner (KATA has no tier number because the odds ratio cannot be calculated). Overall, the data analysis consists of two parts, the first dealing solely with quantitative uncertainty taken into account by statistical methods and the second including the equally important but more subjective sources of uncertainty related to study design, methodology, and applicability to the topic of ETS and lung cancer.

The ETS studies are grouped by country in Table 5-2, which indicates the time period of data collection in each study, sample size, and prevalence of ETS exposure for each study. The geographical distribution of the current epidemiologic evidence is diverse. By country, the number of studies and its percentage of the total number of studies over all countries is as follows: China (4, 13%), England (1, 3%), Greece (2, 6%), Hong Kong (4, 13%), Japan (6, 19%), Scotland (1, 3%), Sweden (2, 6%), United States (11, 35%). (One of the studies from Japan, KATA, does not appear in most of the tables because the odds ratio cannot be calculated.) The studies differ by size, however, which has to be taken into account in analysis. There are two large cohort studies, GARF(Coh) and HIRA(Coh), conducted in the United States and Japan, respectively, and two very small ones, BUTL(Coh) and HOLE(Coh), from the United States and Scotland, respectively. There are two exceptionally large case-control studies--FONT and WUWI of the United States and China; the first was designed specifically to assess the association between ETS and lung cancer, whereas the second has broader exploratory objectives.

Additional characteristics of the case-control studies are summarized in Table 5-3. The table headings are largely self-explanatory, aside perhaps from "ETS sample matched," which refers to whether design matching applies to the ETS subjects (the never-smokers used for ETS/lung cancer analysis). As indicated under "Matched variables," controls are virtually always matched (or at least similar) to cases on age and usually on several other variables as well that the researcher suspects may confound results. The matching often refers to a larger data set than just the ETS subjects, however, because many studies included smokers and investigated a number of issues in addition to whether passive smoking is associated with lung cancer. When the data on

2501031864

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

ETS subjects are extracted from the larger data set, matching is not retained unless smoking status was one of the matching variables. While matching is commonly used as a method to control confounding, there are effective ways available to control confounding in the analysis of the data. For studies that include an "adjusted analysis" (i.e., a statistical method such as poststratification or logistic regression that adjusts the ETS association for potential confounders), the estimated relative risk from that adjusted analysis is compared with the outcome from the crude data alone in Section 5.2.1. The variables taken into account in adjusted analyses differ across studies, depending on study designs and potential confounding addressed by the authors. (Note: "Relative risk" is used to mean estimate of the true [but unknown] relative risk. For case-control studies, the estimate used is the odds ratio. For editorial convenience, relative risk is used for both case-control and cohort studies.)

The selection of the most appropriate relative risk estimate to be used from each study is addressed in Section 5.2.1. In Section 5.2.2, each chosen relative risk estimate is adjusted downward to account for bias expected from some smokers misrepresenting themselves as nonsmokers. This topic has been a contentious issue in the literature for several years, with claims that this one source of systematic upward bias may account entirely for the excess risk observed in epidemiologic studies. Recent detailed investigation of this topic by Wells and Stewart (unpublished) make that claim unlikely (Appendix B). They found that a reasonable correction for bias, calculated on a study-by-study basis, is positive but small. Following this methodology, this report makes reductions in the relative risk estimates at the outset for each study individually prior to statistical inference or pooling estimates from studies from the same country. This is in contrast to the NRC report (1986), which makes the same downward adjustment to all studies (applied to an overall estimate of relative risk obtained after pooling study estimates). The estimates adjusted for smoker misclassification bias are the basis for statistical inference in Section 5.3. The statistical inference approaches consist of both estimation, with confidence intervals, and hypothesis testing, which includes testing for an effect of ETS exposure and for an upward dose-response trend. Section 5.4 considers potential sources of bias and confounding and extends the data interpretation to take these into account. Conclusions are then drawn for hazard identification (i.e., whether ETS is causally associated with increased lung cancer mortality). Chapter 6 of this report addresses U.S. population risk of lung cancer from ETS.

2501031865

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

5.2. RELATIVE RISKS USED IN STATISTICAL INFERENCE

5.2.1. Selection of Relative Risks

Two considerations largely affect the choice of relative risk (RR): (1) whether potential confounders are taken into account and (2) the source and place of ETS exposure used. The alternatives (not yet adjusted for smoker misclassification) are shown by study in Tables 5-4 and 5-5 with the ones selected for analysis in this report in boldface type. Table 5-4 lists the RRs and their confidence intervals, along with explanatory footnotes, and Table 5-5 provides information on source and place of exposure and on the adjusted analysis. Because most studies included spousal smoking, and interstudy comparisons may be useful, spousal smoking was the preferred ETS surrogate except for LAMW and SOBU. In LAMW, spousal smoking data are limited to cases with adenocarcinoma; in SOBU, the data for cohabitants are separate from data for spousal smoking and much of the ETS exposure appears to result from the cohabitants. Only data for broader exposure to ETS than spousal smoking alone were collected in BUFF, CHAN, SVEN, and HOLE(Coh).

After exposure source and place are taken into account in the choice of RR values in Table 5-5, an adjusted RR is considered preferable to a crude RR unless the study review in Appendix A indicates a problem with the adjustment procedure. Of the 31 studies, 20 provide both an adjusted and crude RR, where an "adjusted estimate" is the result of a statistical procedure that takes potential confounding factors into account, usually by stratification or logistic regression. Based on the decision rule just described, our choice of RR is the smaller of the crude and adjusted values in 14 of the 20 studies providing both estimates. In several studies, RR values in addition to those shown in Table 5-5 might be considered (see Table 5-6). They were not found to be the best choices, however, for comparison between studies.

5.2.2. Downward Adjustment to Relative Risk for Smoker Misclassification Bias

There is ample evidence that some percentage of smokers, which differs for current and former smokers, misrepresent themselves as never-smokers (or sometimes the wording of a questionnaire may not be explicit enough to distinguish former smokers from never-smokers) (see Appendix B). It has been argued that the resultant misclassification of some smokers as nonsmokers results in upward bias of the relative risk for lung cancer from ETS exposure (i.e., the observed RR is too large). The essence of the supporting argument is based on smoking concordance between husband and wife--a smoker is more likely than a nonsmoker to have been married to a smoker. Consequently, the smoker misclassified as a nonsmoker is more likely to be

250103186

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

in the ETS-exposed classification as well. Because smoking causes lung cancer, a misclassified smoker has a greater chance of being a lung cancer case than a nonsmoker. The net effect is that an observed association between ETS exposure and lung cancer among people who claim to be never-smokers may be partially explainable by current or former active smoking by some subjects.

The potential for bias due to misreported smoking habits appears to have been noted first by Lee (see discussion in Lehnert, 1984), and it has been emphasized by him in several articles (e.g., Lee 1986, 1987a, 1987b). In Lee (1987b), it is argued that smoker misclassification may explain the entire excess lung cancer risk observed in self-reported never-smokers in epidemiologic studies. Lee's estimates of bias due to smoker misclassification appear to be overstated, for reasons discussed in Appendix B.

The NRC report on ETS (NRC, 1986) devotes considerable attention to the type of adjustment for smoker misclassification bias. It follows the construct of Wald and coworkers, as described in Wald et al. (1986); Wald was the author of this section of the NRC report. An illustrative diagram for the implicit true relative risk of lung cancer from exposure to ETS in women from spousal smoking is shown in Figure 2 of Wald et al. (1986). A similar example is in Table 12-5 of the NRC report.

Both Lee's and Wald's work adjust an overall relative risk estimate, pooled over several studies, downward, rather than address each individual study, with its own peculiarities, separately. Furthermore, statistical analysis over the studies as a whole is conducted first, and then an adjustment is made to the overall relative risk estimate. The recent work of Wells and Stewart (Appendix B) on this subject makes an adjustment to each individual study separately. Consequently, the pertinent adjustment factors that vary by study and type of society can be tailored to each study and then applied to the observed data prior to any statistical analysis. The latter procedure is applied in this report.

The methodology to adjust for bias due to smoker misclassification and the details of its application to the ETS studies are in Appendix B. The results of the adjustment and estimate of bias are given in Table 5-7. In general, the biases are low in East Asia, or in any traditional society such as Greece, where female smoking prevalence is low and the female smoker risk is low. Some of the calculated biases are slightly less than unity when carried to three decimal places. This may result from the assumption in the calculations that there is no passive smoking effect on current smokers.

05/15/92
2501031867

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

5.3. STATISTICAL INFERENCE

5.3.1. Introduction

Table 5-8 lists the values of several statistical measures by study for spousal smoking (see boldface entries in Table 5-5 for details). Their meaning will be described before proceeding to interpretation of the data, even though the concepts discussed may be familiar to most readers. The p-values refer to a test for effect and a test for trend. In the former, the null hypothesis of no association (referred to as "no effect" of ETS exposure on lung cancer risk) is tested against the alternative of a positive association (see Appendix E). The test for trend applies to a null hypothesis of no association between RR and exposure level against the alternative of a positive association. When data are available on more than two levels of intensity or duration of ETS exposure, typically in terms of the husband's smoking habit (e.g., cig./day or years of smoking), then a test for trend is a useful supplement in testing for an effect, as well as indicating whether a dose-response relationship is likely.

The entries under "Power" in Table 5-8 are calculated for the study's ability to detect a true relative risk of 1.5 and a decision rule to reject the null hypothesis of no effect when $p < 0.05$ (see Dupont and Plummer [1990], for methods to calculate power). The power is the estimated probability that the null hypothesis would be rejected if the true relative risk is 1.5 (i.e., that the correct decision would result; the power would be larger if the true relative risk exceeds 1.5). Using the estimates of power for the U.S. studies in Table 5-8 for illustration, the estimated probability that a study would *fail* to detect a true relative risk of 1.5 (equal to 1-power, the probability of a Type II error [discussed in the next paragraph] when the true relative risk is 1.5) is as follows: FONT, 0.07; GARF(Coh), 0.08; GARF, 0.40; JANE, 0.56; BUFF, 0.83; CORR, 0.78; WU, 0.79; HUMB, 0.80; KABA, 0.83; BUTL(Coh), 0.82; BROW, 0.85. Thus, 7 of the 11 U.S. studies have only about a 20% chance of detecting a true relative risk as low as 1.5, when taken alone. Sources of bias effectively alter the power in the same direction as the bias (e.g., a downward bias in RR will increase the expected p-value, i.e., reduce significance, in a test for effect). Of the potential sources of bias discussed by study in Appendix A, the predominant direction of influence on the observed RR, when identifiable, appears to be in the direction of unity, thus affecting power adversely. The RRs have already been reduced to adjust for smoker misclassification, the only systematic source of upward bias that has been established.

Studies of all sizes, large and small, are equally likely to make a false conclusion if ETS is not associated with lung cancer risk (Type I error). However, smaller studies are less likely to detect a real association when there is one (Type II error). This imbalance comes from using the

250103186B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

significance level of the test statistic to determine whether to reject the null hypothesis. If the decision rule is to reject the hypothesis when the p-value is smaller than some prescribed value (e.g., 0.05), then the Type I error rate is 0.05, but the Type II error rate increases. When a study with low power fails to reject the null hypothesis of no effect, it is not very informative because, if the power is low, that outcome may be nearly as likely when the null hypothesis is false as when it is true. When detection of a small relative risk is consequential, pooling informational content of suitably chosen studies empowers the application of statistical methods.

The heading in Table 5-8 that remains to be addressed is "Relative weight," to be referred to simply as "weight." When the estimates of relative risk from selected studies are combined, as for studies within the same country as shown in the table, the logarithms of the RRs are weighted inversely proportional to their variances (see Appendix E and Footnote 2 of Table 5-8). These relative weights are expressed as percentages summing to 100 for each country in Table 5-8. Study weight and power are positively associated, which is explained by the significant role of study size to both. Consequently, studies weighted most heavily (because the standard errors of the RRs are low) also tend to be the ones with the highest power (most likely to detect an effect when present).

5.3.2. Outcomes by Study and Country

5.3.2.1. *Tests for Association*

The p-values of the test statistics for the hypothesis of no effect (i.e., RR = 1) are shown in Table 5-8. Values of the test statistics (the standardized log odds ratio; see Appendix E) are plotted in Figure 5-1. Also shown in Figure 5-1 for reference are the points on the horizontal axis corresponding to p-values of 0.5, 0.2, 0.1, 0.05, 0.01, and 0.001. For example, the area under the curve to the right of the vertical line labeled p = 0.01 is 0.01 (1%), so it is apparent from Figure 5-1 that three studies had significance levels $p < 0.01$ (more specifically, $0.001 < p < 0.01$. The size of the symbol (upside-down triangle) used for a study is proportional in area to the relative weight of that individual study, but of current interest is the location and not the size of the symbol. If the null hypothesis is true, then the plotted values would arise from a standard normal distribution, shown in the figure (points to the left of zero indicate that the RR is less than 1 and points to the right of zero indicate that RR is greater than 1). If the points lie more toward the right side of the normal curve than would be likely to occur by chance alone, then the hypothesis of no effect is rejected in favor of a positive association between ETS exposure and lung cancer. If one constructs five intervals of equal probability (i.e., intervals of equal area

250103186

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

under the standard normal curve), the expected number of observations in each interval is six (these five intervals are not shown on Figure 5-1). The observed numbers in these intervals, however, for intervals from left to right are 3, 3, 1, 7, and 16, an outcome that is significant at $p < 0.005$, by the chi-squared goodness-of-fit test. At the points on the standard normal curve corresponding to p-values 0.5, 0.4, 0.3, 0.2, 0.1, and 0.05, the probability that a number of outcomes as large as that actually observed would occur by chance is less than 0.005 at all points. Consequently, the hypothesis of no effect is rejected on statistical grounds, and that conclusion is not attributable to a few extreme outcomes that might be aberrant in some way.

Figure 5-2 displays the U.S. studies alone (see Appendix E for calculation of the test statistics). Figure 5-3 corresponds to Figure 5-1 except that the test statistics for the hypothesis of no effect (i.e., RR = 1) for the significance levels shown apply to a single overall estimate of RR for each country, formed by statistically pooling the outcomes from the studies within each country. The areas of the symbols for countries are also in proportion to statistical weight as given in Table 5-8. It is implicitly assumed that studies within a country, and the subpopulations sampled, are sufficiently homogeneous to warrant to combine their statistical results into a single estimate for the country (see S. Greenland [1987] for a discussion of applications of meta-analysis to epidemiology). The calculational method employed weights the observed RR from each study within a country inversely proportional to its estimated variance (see Appendix E). The relative study weights are shown in Table 5-8. Each symbol in Figures 5-1, 5-2, 5-3, and 5-4 has been scaled so that its area is proportional to the weight of the outcome represented, relative to all other outcomes shown in the same figure.

Greece, Hong Kong, and Japan, which together comprise a total weight of 39%, are *each* statistically significant at $p < 0.01$ against the null hypothesis of no increase in relative risk (RR = 1). When the United States is included, the total weight is 73%, and *each* of the four countries is significant at $p < 0.02$. The four studies combined into the group called Western Europe are not large. Together they represent 5% of the total weight, and their combined odds ratio (1.17) is slightly above 1 but not statistically significant ($p = 0.21$). In contrast, China is weighted quite high (22%), the p-value is large (0.66), and the odds ratio is less than 1 (0.95), strongly indicating no evidence of an increase in RR due to ETS. This is largely because China is very heavily influenced by WUWI (relative weight of 60%), which is a very large case-control study. However, this apparent inconsistency in WUWI may be due to the presence of indoor smoke from cooking and heating which may mask any effect from passive smoking. A similar but more extreme situation is found in LIU, conducted in a locale where indoor heating with smokey

250103187D

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

coal (an established risk factor for lung cancer) and inadequate venting are common. The indoor environments of the populations sampled in WUWI and LIU make detection of any carcinogenic hazard from ETS unlikely, and thus render these studies to be of little value for that purpose (see discussions of WUWI and LIU in Appendix A). Without WUWI or LIU, the combined results of the two remaining studies in China, GAO and GENG, are significant at p = 0.03, as shown in Table 5-8 and pictured in Figure 5-4.

5.3.2.2. ***Confidence Intervals***

Confidence intervals for relative risk are displayed by study and by country in Table 5-8 (see Appendix E for method of calculation). The 90% confidence intervals by country are illustrated in Figure 5-5. (Note: 90% confidence intervals are used for correspondence to a right-tailed test of the hypothesis of no effect at a 5% level of significance.) The area of the symbol (solid circle) locating the point estimate of relative risk within the confidence interval is proportional to study weight. Symbol size is used as a device to draw attention to the shorter confidence intervals, which tend to be based on more data than the longer ones. The confidence intervals for countries jointly labeled as Western Europe are in Table 5-8, except for Sweden which contains two studies, PERS and SVEN. For those two combined, the odds ratio (OR) is 1.19 (90% C.I. = 0.81-1.74). The confidence interval for China without LIU or WUWI (i.e., including only GAO and GENG) is displayed in Figure 5-6.

In descending order, the relative risks in Figure 5-6 are for Greece, Hong Kong, Japan, China, the United States, and Western Europe. Values in the interval (1.43, 1.71) are contained in the 90% confidence intervals of the first four countries (Greece, Hong Kong, Japan, and China), where the observed relative risks range from 2.00 down to 1.36. The region in common to the confidence intervals for the two remaining countries or groups of countries, United States and Western Europe, is (1.04, 1.35), the interval for the United States alone. The observed relative risks are close (1.19 and 1.17). If the United States and Western Europe are combined, the RR is 1.18 (90% C.I. = 1.05-1.34). The estimated relative risks from exposure to spousal smoking differ between countries, with Greece and the Asian countries near the high end of the scale and the Western countries, United States and Western Europe, at the low end. However, the relative risks only pertain to ETS exposure from spousal smoking which may be a higher proportion of total ETS exposure in some countries than in others. This emphasizes the importance of taking into account exposure and background (nonspousal) ETS as used, which is considered in the estimation of population risk for the United States in Chapter 6.

250103187

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

5.3.2.3. *Tests for Trend*

When epidemiologic data for the "exposed" group are available for two or more exposure levels plus the control group, a test for trend can be used to test for a dose-response relationship. A dose-response relationship increases support for a causal association by diminishing the likelihood that the results can be explained by confounding. Furthermore, when low exposure levels have little effect on the observed RR but the RR does increase with increasing exposure, a trend test may be able to detect an association that would be masked in a test for effect. This is especially likely to occur when dealing with a weak association or crude surrogate measures for exposure (i.e., greater potential for misclassification), both of which are difficulties in studies of ETS and lung cancer.

As discussed in Chapter 3, ETS is a dilute mixture. Furthermore, questionnaire-based assessment of exposure to ETS is a crude indicator of actual lifetime exposure, and spousal smoking is an incomplete surrogate for exposure because it does not consider ETS from other sources, such as the workplace. Under these circumstances, there is considerable potential for exposure misclassification, which is compounded when the exposed group is further divided into level-of-exposure categories. Division into exposure-level categories also reduces the power to statistically determine a real effect by decreasing the number of subjects in an exposure group. This is especially problematic in small studies. These inherent difficulties with the ETS database would tend to diminish the possibility of detecting dose-response relationships. Therefore, the inability to demonstrate a dose-response trend is not considered evidence against causality; rather, if a statistically significant trend can be detected despite these potential obstacles, it provides evidential support of a causal association.

Table 5-9 presents the dose-response data and trend test results for females currently available from the studies of ETS and lung cancer discussed in this report. Exposure is measured by intensity (e.g., cig./day smoked by the husband), duration (e.g., number of years married to a smoker), or a combination of both (e.g., number of pack-years--packs per day x years of smoking by the husband). The p-values reported in the table are for a test of no trend against the one-sided alternative of an upward trend (i.e., increasing RR with increasing exposure). (Note: The results for tests of trend are taken from the study reports. Unless the report specified that a one-sided alternative was used, the reported p-value was halved to reflect the outcome for the one-sided alternative of RR increasing with exposure. Where the data are available, the p-values reported by the individual study's authors have been verified here by application of the Mantel-Haenszel test [Mantel and Haenszel, 1963].)

250103187Z

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Wu-Williams and Samet (1990) previously reviewed the dose-response relationships from the epidemiologic studies on ETS then available. They determined that 12 of 15 studies were statistically significant for the trend test for at least one exposure measure. The probability of this proportion of statistically significant results occurring by chance in this number of studies is virtually zero ($p < 10^{-13}$). Intensity of spousal smoking was the most consistent index of ETS exposure for the demonstration of a dose-response relationship.

Our assessment of the dose-response data is similar and provides essentially the same results for a slightly different set of studies. Table 5-10 summarizes the p-values of the trend tests for the various ETS exposure measures from the studies presented in Table 5-9. The exposure measure most commonly used was intensity of spousal smoking. Seven of the eleven studies that reported dose-response data based on cigarettes per day showed statistical significance at the $p < 0.05$ level for the trend test. Again, the probability of this many statistically significant results occurring by chance in this number of studies is virtually zero ($p < 10^{-6}$). The trend test results for the other exposure measures were consistent, in general, with those based on cigarettes per day (three of six studies using total years of exposure were significant, as were two of two studies using pack-years).

Overall, 10 of the 15 studies with test for trend are statistically significant for one or more exposure measures. These results are especially compelling in view of the fact that dividing the data into smaller exposure categories decreases the power to detect a real effect. No possible confounder has been hypothesized that correlates with ETS exposure and could explain the increasing incidence of lung cancer with increasing exposure to ETS in so many independent studies from different countries.

By country, the number of studies with significant results for upward trend is: China, 1 of 2; Greece, 2 of 2; Hong Kong, 1 of 2; Japan, 3 of 3; Sweden, 0 of 1; and United States, 3 of 5. Of particular interest, two of the U.S. studies, GARF and CORR, are statistically significant for a test of trend, providing evidence for an association between ETS exposure and lung cancer even though neither was significant in a test for effect. This occurs because in both cases, the data supporting an increase in RR are largely at the highest dose level. It might be that relatively high exposure levels are necessary to detect an effect in the United States, as would be expected if spousal smoking is a weaker surrogate for total ETS exposure in this country, a possibility mentioned previously. The U.S. study by Fontham et al. (1991), a well-conducted study and the largest case-control study of ETS and lung cancer to date, with the greatest power of all the U.S. studies to detect an effect, was statistically significant with a p-value of 0.04 for the trend test

250103187 3

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

with pack-years as the exposure measure. When the analysis was restricted to adenocarcinomas, the majority of the cases, tests for trend were statistically significant by both years ($p = 0.02$) and pack-years ($p = 0.01$).

5.3.2.4. *Statistical Conclusions*

Two types of tests have been conducted: (1) a test for effect, wherein subjects must be classified as exposed or unexposed to ETS, generally according to whether the husband is a smoker or not, and (2) a trend test, for which exposed subjects are further categorized by some level of exposure, such as the number of cigarettes smoked per day by the husband, duration of smoking, or total number of packs smoked. Results are summarized in Table 5-11, with countries in the same order as in Table 5-8. Studies are noted in boldface if the test of effect or the trend test is significant at 0.1, or if, as in PERS, the odds ratio at the highest exposure is significant. In 9 of the 11 studies in Greece, Hong Kong, or Japan, at least one of the tests is significant at 0.1. In 8 of these 11 studies, at least one of the tests is significant at 0.05. For the United States and Western Europe, the corresponding numbers of studies are only 6 and 5 of 15. For the studies within the first group of countries (Greece, Hong Kong, and Japan), the median power is 0.43, and only 1 of the 10 studies (10%) has power less than 0.25 (INOU). By contrast, the median power for the U.S. and Western Europe together is 0.21, and 10 of the 15 studies (67%) have power less than 0.25. Significance is meaningful in a small study, but nonsignificance is not very informative because there is little chance of detecting an effect when there is one. Consequently, there are several studies in the United States-Western Europe group that provide very little information. One of the four studies in China is significant, at both the 0.1 and 0.05 levels. Two of the three nonsignificant studies in China (LIU and WUWI) are not very informative on ETS for reasons previously described.

For the U.S. and Western Europe studies, 3 of the 5 with power greater than 0.25 are shown in boldface (FONT, GARF, and PERS), indicating at least suggestive evidence of an association between ETS and lung cancer, compared to only 3 of 10 with power under 0.25 (CORR, HUMB, and WU). The test of effect is suggestive for CORR and HUMB (p-values of 0.09 and 0.10, respectively), and CORR is positive for trend (p-value of 0.02) with an observable upward dose-response pattern. FONT is significant for effect (p-value = 0.04) and trend (p-value = 0.04) with observable dose-response (both p-values are for all cell types). Neither GARF nor PERS are significant for effect, but both are significant in other tests (GARF, p-value of 0.03 for trend; PERS, p-value of 0.02 at the high dose). The significance in CORR, GARF,

250103187A

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

and PERS appears to result from an increase in the observed relative risk at the highest exposure level. Overall, the evidence of an association is stronger in the United States and Western Europe than appears from the test for effect alone.

To summarize, there is substantial statistical evidence that exposure to ETS from spousal smoking is associated with increased lung cancer mortality in Greece, Hong Kong, Japan, and the United States. The association for Western Europe appears similar to that in the United States, but not as much statistical evidence has accumulated there. The usefulness of statistical information from studies in China is limited, so no firm conclusions are drawn from the studies there. The statistical evidence is also conclusive from the individual studies, without combining studies within each country to gain power to detect an effect. The number of significant outcomes in either the test for effect, or the test for trend, in Table 5-11 is not attributable to chance alone. Tests for effect and for trend are jointly supportive of the same conclusion. Adjustment on an individual study basis for potential bias due to smoker misclassification results in slightly lower relative risk estimates but does not affect the overall conclusions.

5.4. EXTENDED DATA INTERPRETATION

5.4.1. Introduction

Whereas Section 5.3 examined the epidemiologic data by individual study and by pooling all studies by country, this section analyzes the data in three additional ways. First, it assesses the impact of six potential confounders on the results (Section 5.4.2). Then, in Section 5.4.3, this report examines the possible sources of bias and other uncertainty-related design features inherent in case-control studies to determine whether there are any systematic sources of bias (other than smoker misclassification bias addressed in Section 5.2) that might affect the observed results. The third extended analysis approach judges the comparative quality of the individual studies according to how well they have been able to control for these potential biases and confounders and categorizes each study into one of four tiers (Section 5.4.4). This separation of studies into tiers is used in the statistical analysis presented in Section 5.4.5 to determine whether the studies with higher utility provide different conclusions.

The element of chance has been taken into account by the statistical methods previously applied. It remains to consider potential sources of bias and confounding and whether an association between ETS exposure and lung cancer may be causally related. Validity is the most relevant concern for hazard identification. Generalizability of results to the national population (depending on "representativeness" of the sample population, treated in the text) is important for

250103187S

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

the characterization of population risk, but no more so than validity. As stated by Breslow and Day (1980), "In an analysis, the basic questions to consider are the degree of association between risk for disease and the factors under study, the extent to which the observed associations may result from bias, confounding and/or chance, and the extent to which they may be described as causal."

Confounding requires the presence of a non-ETS cause of lung cancer associated with ETS exposure. Candidate confounders included in the ETS studies are reviewed in the next section. Attention is then turned to methodological issues of data classification, collection, and analysis that may produce bias or inadequate control for confounding. Potential bias and confounding in each study is discussed vis-a-vis its statistical outcome in Table 5-11, based on the detailed reviews in Appendix A. In addition, each study is assigned to one of four tiers, depending on the review. Tier 1 studies are those of greatest utility for investigating a potential association between ETS and lung cancer. Other studies are assigned to Tiers 2, 3, and 4 as confidence in their utility diminishes. Tier 4 is reserved for studies we would exclude from analysis for ETS, for various reasons specified in the text. The summary RR for each country is then recalculated for studies in Tier 1 alone and for Tiers 1-2, 1-3, and 1-4 (the last category corresponds to Table 5-11). This exercise provides some idea of the extent to which the summary RR for a country depends on the choice of studies. The outcome is used to assess the epidemiologic weight-of-evidence for hazard identification. The concluding section of this chapter draws on the previous statistical analysis and the material in this chapter to formulate conclusions regarding the association of ETS exposure with lung cancer and the evidence supporting causality.

Our objective is to consider the influence of sources of uncertainty on the statistical measures summarized in Table 5-11, although there are limitations to such an endeavor. For example, not controlling for a potential confounder such as age in the statistical analysis, which should be done whether or not the study design is on age, may require reanalyzing data not included in the study report. Potential sources of bias are just that--*potential*--and their actual effect may be impossible to evaluate (e.g., selection bias in case-control studies). Although numerous questions of interest cannot be answered unequivocally, or even without a measure of subjective judgment, it is nevertheless worthwhile to consider issues that may affect interpretation of the quantitative results. The issues of concern are largely those of epidemiologic investigations in general that motivate the conscientious investigator to implement sound methodology. Statistical uncertainty aside, the outcomes of studies that fare well under close examination inspire more confidence and thus deserve greater emphasis than those that do poorly.

250103187G

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Preliminary to the next sections, some relevant notes on epidemiologic concepts are excerpted from two IARC volumes entitled *Statistical Methods in Cancer Research* (Breslow and Day, 1980 and 1987), dealing with case-control and cohort studies, respectively, which are excellent references. In the interest of brevity, an assortment of relevant passages is simply quoted directly from several locations in the references (page numbers and quotation marks have been omitted to improve readability). Some readers may wish to skip to the next section; those interested in a more fluid, cogent, and thorough presentation are referred to the references.

> Bias and confounding. The concepts of bias and confounding are most easily understood in the context of cohort studies, and how case-control studies relate to them. Confounding is intimately connected to the concept of causality. In a cohort study, if some exposure E is associated with disease status, then the incidence of the disease varies among the strata defined by different levels of E. If these differences in incidence are caused (partially) by some other factor C, then we say that C has (partially) confounded the association between E and the disease. If C is not causally related to disease, then the differences in incidence cannot be caused by C, thus C does not confound the disease/exposure association.
>
> Confounding in a case-control study has the same basis as in a cohort study . . . and cannot normally be removed by appropriate study design alone. An essential part of the analysis is an examination of possible confounding effects and how they may be controlled.
>
> Bias in a case-control study, by contrast, [generally] arises from the differences in design between case-control and cohort studies. In a cohort study, information is obtained on exposures before disease status is determined, and all cases of disease arising in a given time period should be ascertained. Information on exposure from cases and controls is therefore comparable, and unbiased estimates of the incidence rates in the different subpopulations can be constructed. In case-control studies, however, information on exposure is normally obtained after disease status is established, and the cases and controls represent samples from the total. Biased estimates of incidence ratios will result if the selection processes leading to inclusion of cases and controls in the study are different (selection bias) or if exposure information is not obtained in a comparable manner from the two groups, for example because of differences in response to a questionnaire (recall bias). Bias is thus a consequence of the study design, and the design should be directed towards eliminating it. The effects of bias are often difficult to control in the analysis, although they will sometimes resemble confounding effects and can be treated accordingly.
>
> To summarize, confounding reflects the causal association between variables in the population under study, and will manifest itself similarly in both cohort and case-control studies. Bias, by contrast, is not a property of the underlying population. It results from inadequacies in the design of case-control studies, either in the selection of cases or controls or from the manner in which the data are acquired.

> On prospective cohort studies. One of the advantages of cohort studies over case-control studies is that information on exposure is obtained before disease status is ascertained. One can therefore have considerable confidence that errors in

05/15/92
2501031877

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

measurement are the same for individuals who become cases of the disease on interest, and the remainder of the cohort. The complexities possible in retrospective case-control studies because of differences in recall between cases and controls do not apply. [Regarding the success of a cohort study, the] follow-up over time . . . is the essential feature. . . . The success with which the follow-up is achieved is probably the basic measure of the quality of the study. If a substantial proportion of the cohort is lost to follow-up, the validity of the study's conclusions is seriously called into question.

On case-control studies. . . . despite its practicality, the case-control study is not simplistic and it cannot be done well without considerable planning. Indeed, a case-control study is perhaps the most challenging to design and conduct in such a way that bias is avoided. Our limited understanding of this difficult study design and its many subtleties should serve as a warning--these studies must be designed and analyzed carefully with a thorough appreciation of their difficulties. This warning should also be heeded by the many critics of the case-control design. General criticisms of the design itself too often reflect a lack of appreciation of the same complexities which make these studies difficult to perform properly.

The two major areas where a case-control study presents difficulties are in the selection of a control group, and in dealing with confounding and interaction as part of the analysis. . . . these studies are highly susceptible to bias, especially selection bias which creates non-comparability between cases and controls. The problem of selection bias is the most serious potential problem in case-control studies. . . . Other kinds of bias, especially that resulting from non-comparable information from cases and controls are also potentially serious; the most common of these is recall . . . bias which may result because cases tend to consider more carefully than do controls the questions they are asked or because the cases have been considering what might have caused their cancer.

5.4.2. Potential Confounders

In addition to standard demographic risk factors (e.g., age) that are frequently either adjusted for or controlled for by study design, a number of other variables have been considered as potential risk factors for lung cancer and thus confounders of the ETS-lung cancer association. In the following discussion, relevant findings from the ETS studies are summarized for six general categories: (1) personal history of lung disease, (2) family history of lung disease, (3) heat sources, (4) cooking with oil, (5) occupation, and (6) diet. Table 5-12 provides an overview of results in these categories. Two shortcomings are common in the statistical inference of nonspousal ETS factors: failure to control for the potential confounding effects of other factors, including ETS exposures other than from spousal smoking, and failure to adjust significance levels for multiple comparisons. Multiple tests on the same data increase the chance of a false positive (i.e., outcomes appear to be more significant than warranted due to the multiple comparisons being made on the same data).

250103878

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

5.4.2.1. *History of Lung Disease*

Results regarding history of lung disease have been reported in eight of the reviewed ETS studies, but with little consistency. Tuberculosis (TB), for example, is significantly associated with lung cancer in GAO (OR = 1.7; 95% C.I. = 1.1 - 2.4) but not in SHIM (OR = 1.1, no other statistics), LIU or WU (no ORs provided). Chronic bronchitis, on the other hand, is nonsignificant in GAO (OR = 1.2; 0.8 - 1.7), SHIM (OR = 0.8), KABA, and WU, but is highly significant in LIU (OR = 7.37; 2.40 - 22.66 for females; OR = 7.32; 2.66 - 20.18 for males) and mildly so in WUWI (OR = 1.4; 1.2 - 1.8). (Notably, both the LIU and WUWI populations were exposed to non-ETS sources of household smoke.) Consideration of each lung disease separately, as presented, ignores the effect of multiple comparisons described above. For example, GAO looked at five categories of lung disease. If that were taken into account, the confidence interval for TB would no longer indicate significance. No discussion of the multiple comparisons effect was found in any of the references, which should at least be acknowledged.

Broadening our focus to examine the relationship of lung cancer to history of lung disease in general does little to improve consistency. GENG reports an adjusted OR of 2.12 (1.23 - 3.63) for history of lung disease, GAO's disease-specific findings are consistently positive, and WUWI reports three positive associations out of an unknown number assessed. SHIM and WU, however, consistently found no effect except marginally for silicosis (perhaps better construed as an occupational exposure surrogate) in SHIM and for childhood pneumonia in WU. LIU found a significant association only for chronic bronchitis and KABA only for pneumonia. Interpretation is hampered by the lack of numerical data for factors that were not statistically significant in KABA, LIU, and WU. Even with such data, however, interpretation is hampered by the absence of control for key potential confounders in many of the studies (e.g., age in GENG and LIU). Only one study (WU) attempted to control for a history variable (childhood pneumonia), which reportedly did not alter the ETS results. The importance of prior lung disease as a potential confounder in studies of ETS is thus unclear, but it does not appear to distort results one way or the other.

5.4.2.2. *Family History of Lung Disease*

Only a few of the studies addressed family history of lung disease as a potential risk factor for lung cancer. GAO found no significant association between family history of lung cancer and subjects' disease status (e.g., parental lung cancer OR = 1.1; 95% C.I. = 0.6 - 2.3), and positive family histories were very rare (e.g., 1.0% among mothers of either cases or controls). In contrast,

250103187

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

WUWI reports a significant association with history of lung cancer in first-degree relatives (OR = 1.8; 1.1 - 3.0), which occurred in about 4.5% of the cases. The presence of TB in a household member (OR = 1.6; 1.2 - 2.1) is also significant, even after adjustment for personal smoking and TB status. The rarity of family-linked lung cancer in these populations makes accurate assessment difficult and also reduces the potential impact on results of any effect it may have. Its study in populations where such cancer is more common would be more appropriate. The household TB outcome may be the result of multiple comparisons and/or confounding, particularly in view of the weaker (nonsignificant) outcome noted for *personal* TB status.

5.4.2.3. *Heat Sources for Cooking or Heating*

Household heating and cooking technologies have received considerable attention as potential lung cancer risk factors in Asian ETS studies. Most studies have focused on fuel type. Kerosene was specifically examined in three studies. All three found positive associations--CHAN and LAMW for kerosene cooking, and SHIM for kerosene heating--but none of the associations were statistically significant, and the SHIM relationship held only for adult and not for childhood exposure. Five studies specifically examined coal. GENG evaluated use of coal for cooking and found a significant positive association. Use of coal for household cooking or heating prior to adulthood is significantly associated with lung cancer in WU's study of U.S. residents, but no results for adulthood are mentioned. Recent charcoal stove use showed a positive (OR = 1.7) but not significant association in SHIM. Separate analyses of five coal-burning devices and two non-coal-burning devices by WUWI found positive though not always significant associations for the coal burners. In contrast, SOBU found no association between use of unventilated heating devices--including mostly kerosene and coal-fueled types but also some wood and gas burners--and lung cancer (OR = 0.94 for use at age 15, 1.09 at age 30, 1.07 at present). Results for wood or straw cooking were specifically reported in three studies. SOBU found a significant association for use of wood or straw at age 30 (OR = 1.89; 95% C.I. = 1.16 - 3.06) but only a weak relationship at age 15. GAO found no association with current use of wood for cooking (OR = 1.0; 0.6 - 1.8), and WUWI mentions that years of household heating with wood, central heating, and coal showed nonsignificant trends (negative, negative, and positive, respectively).

Overall, studies that examined heating and cooking fuels generally found evidence of an association with lung cancer for at least one fuel, which was usually but not always statistically significant. Such relationships appeared most consistently for use of coal and most prominently in WUWI and LIU. Neither study found a significant association between ETS and lung cancer, nor

250103188O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

did either address whether coal use was associated with ETS exposure. The presence of non-ETS sources of smoke within households, however, may effectively mask detection of any effect due to ETS (as noted by the authors of WUWI). Evidence of effects of other fuel types and devices is more difficult to evaluate, particularly because many studies do not report results for these factors, but kerosene-fueled devices seem worthy of further investigation.

5.4.2.4. *Cooking With Oil*

Cooking with oil was examined by GAO and WUWI, both conducted in China, with positive associations for deep-frying (OR ranges of 1.5-1.9 and 1.2-2.1, respectively, both increasing with frequency of cooking with oil). GAO also reports positive findings for stir-frying, boiling (which in this population often entails addition of oil to the water), and smokiness during cooking and found that most of these effects seemed specific for users of rapeseed oil. These results may apply to other populations where stir-frying and certain other methods of cooking with oil are common. Neither study, however, addressed whether cooking with oil is associated with ETS and thus may confound the effect attributed to ETS.

5.4.2.5. *Occupation*

Seven studies investigated selected occupational factors, with five reporting positive outcomes for one or more occupational variables. The outcomes appear somewhat inconsistent, however. SHIM found a strong and significant relationship with occupational metal exposure (OR = 4.8) and a nonsignificant one with coal, stone, cement, asbestos, or ceramic exposure, while WUWI found significant positive relationships for metal smelters (OR = 1.5), occupational coal dust (OR = 1.5), and fuel smoke (OR = 1.6) exposure. Textile work is positively associated with lung cancer in KABA and negatively in WUWI. BUFF divided occupations into nine categories plus housewife and found eight positive and one negative associations relative to housewives, but only one ("clerical") is significant. GAO, on the other hand, found no association with any of six occupational categories, while GENG found a significant association for an occupational exposure variable that encompassed textiles, asbestos, benzene, and unnamed other substances (OR = 3.1; 1.58 - 6.02). WU reported "no association between any occupation or occupational category," although there was a nonsignificant excess among cooks and beauticians. Finally, BUTL(Coh) found an increased RR for wives whose husbands worked in blue collar jobs (> 4; never-smoker). HIRA(Coh) did not present findings for husband's occupation as a risk factor independently but reported that adjustment for this factor did not alter the study's ETS results. Few studies

250103188

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

attempted to adjust ETS findings for occupational factors--SHIM found only modest effects of such adjustment for occupational metal exposure, despite an apparent strong independent effect for this factor, and GENG found only minimal effect of occupational exposure on active smoking results but did no adjustment of ETS results. Overall, multiple comparisons, confounding by other factors (e.g., socioeconomic status, age), and the rarity of most specific occupational exposure sources probably account for the inconsistent role of occupation in these studies.

5.4.2.6. *Dietary Factors*

Investigations related to diet have been reported in six of the ETS studies, with mixed outcomes. The fundamental difficulty lies in obtaining accurate individual values for key nutrients of interest such as β-carotene. The relatively modest size of most ETS study populations adds further uncertainty in attempts to detect and assess any dietary effect that, if present, is likely small. In those studies where dietary data were collected and adjusted for in the analysis of ETS, diet has had no significant effect. Nevertheless, diet has received attention in the literature as a potential confounder, or source of bias, for ETS (e.g., Koo, 1988; Koo et al., 1988; Sidney, 1989; Butler, 1990, 1991; Marchand et al., 1991), so a more detailed and specific discussion is provided in this section.

Diet is of interest for a potential protective effect against lung cancer, unlike more typical potential confounders that *cause* lung cancer. If nonsmokers unexposed to passive smoke have a lower incidence of spontaneous (unrelated to tobacco smoke) lung cancer incidence due to a protective diet, then the effect would be upward bias in the RR for ETS. However, for diet to *explain* fully the significant association of ETS exposure in Greece, Hong Kong, Japan, and the United States, which differ by diet as well as other lifestyle characteristics, it would need to be shown that in *each* country: (1) there is a diet protective against lung cancer from ETS exposure, (2) diet is inversely associated with ETS exposure, and (3) the association is strong enough to produce the observed relationship between ETS and lung cancer. Diet may modify the magnitude of any lung cancer risk from ETS (conceivably increase or decrease risk, depending on dietary components), but that would not affect whether ETS is a lung carcinogen.

The literature on the effect of diet on lung cancer is not consistent or conclusive, but taken altogether there may be a protective effect from a diet high in β-carotene, vegetables, and possibly fruits. Also there is some evidence that low consumption of these substances may correlate with increased ETS exposure, although not necessarily for all study areas. The calculations made by Marchand et al. (1991) and Butler (1990, 1991) are largely conjectural, being

250103188

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

based only on *assumed* data. Therefore, we examined the passive smoking studies themselves for empirical evidence on the effect of diet and whether it may affect ETS results.

It was found that nine of the studies have data on diet, although only five of the them use a form of analysis that assesses the impact of diet on the ETS association. None of those five (CORR, HIRA[Coh], KALA, SHIM, and SVEN) found that diet made a significant difference. In the four studies where data on diet were collected but not controlled for in the analysis of ETS, three (GAO, KOO, and WUWI) are from East Asia and one (WU) is from the United States. Koo (1988a), who found strong protective effects for a number of foods, has been one of the main proponents of the idea that diet may explain the passive smoking lung cancer effect. To our knowledge, however, she has not published a calculation examining that conjecture in her own study where data were collected on ETS subjects. In WU, a protective effect of β-carotene was found, but the data include a high percentage of smokers (80% of the cases for adenocarcinoma, 86% for squamous cell) and the number of never-smokers is small.

The equivocal state of the literature regarding the effect of diet on lung cancer is also apparent in the nine ETS studies that include dietary factors, summarized in Table 5-13. Note that GAO found an adverse effect from β-carotene and no one found it protective. HIRA and KOO found opposite effects from fish while SHIM found no effect. Fruit was found to be protective by KALA and KOO but adverse by SHIM and WUWI. Retinol (based on consumption of eggs and dairy products) was found to be protective by KOO but adverse by GAO and by WUWI.

In view of the results summarized in Tables 5-12 and 5-13, the actual data of ETS studies do not support the suspicion that diet introduces a systematic bias in the ETS results. Indeed, it would be difficult to show otherwise. Dietary intake is difficult to assess; dietary habits vary within countries and enormously between countries, making it difficult to attribute any effect on lung cancer to a particular food group; lifestyle characteristics and consumption of food and beverage with possibly an adverse effect may be associated, either positively or negatively, with the food group under consideration. The potential for bias and particularly for confounding is high; an effect on lung cancer rate is probably small, requiring sizable samples and meticulous design for reliable results; exposure to other known risk factors for lung cancer needs to be carefully controlled. It would, of course, be helpful to identify dietary factors that may affect lung cancer, positively or negatively, because that information could usefully contribute to public health. To affect interpretation of ETS results, however, it would need to be established also that

2501031883

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

consumption of the dietary factor of interest is highly correlated with ETS exposure in study populations where ETS exposure is linked with increased incidence of lung cancer.

5.4.2.7. *Summary on Potential Confounders*

In summary, an examination of potential confounding factors finds no factor that can explain the association between lung cancer and ETS exposure observed by independent investigators across several countries that vary in social and cultural behavior, diet, and the presence of other potential confounders. On the other hand, the high levels of indoor air pollution from other sources (e.g., smokey coal) that occur in some parts of China and show statistical associations with lung cancer in the studies of WUWI and LIU may mask any ETS effect in those studies.

5.4.3. Potential Sources of Bias and Other Uncertainty

Some of the major areas contributing to study limitations and uncertainty are shown in Table 5-14 (in two parts, 14A and 14B) with an indication of which studies may be affected. Although each study has its own individual strengths and weaknesses, this table provides an overview and index, of sorts, to the detailed reviews in Appendix A for the topics shown. The table headings are broadly categorized under classification (selection and classification of subjects and data), collection (sources and methods of data collection), and analysis (methods and topics related to data analysis). The subheadings are described below. The likely direction of the bias is indicated when apparent.

"ETS Subjects" refers to classification of candidates as nonsmokers, generally never-smokers. A study is included under this heading if the restriction on prior smoking is not explicit, is perhaps too lenient (e.g., may have smoked regularly for up to 6 months), or males are included with females in the analysis (JANE only). Former smoking is a source of upward bias (i.e., away from the null hypothesis). "ETS Exposure" refers to the criteria for classifying ETS subjects as exposed or unexposed. Studies under this heading typically do not distinguish as sharply as they might, resulting in downward bias (i.e., toward the null hypothesis). ("Errors of measurement in the exposure variables . . . reduce the apparent risk, unless the errors are linked in some unusual manner to confounding variables," Breslow and Day, 1980, p. 114).

Inclusion of misdiagnosed cases also produces a downward bias. Studies for which the methods of diagnosis (or confirmation, if performed) of cell type are either not indicated or are not designated exclusively by histology or cytology are listed under "Cases" in Table 5-14A. The

25010318B4

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

distribution of diagnosis methods is shown in Table 5-15. BROW, WU, and TRIC are included under cases because they are restricted by cell type for which the bias is unknown.

As indicated above, the selection of the control group is one of the most important and difficult tasks in a case-control study. Quoting Breslow and Day (1980), "There is no one type of control group suitable for all studies and, it must be acknowledged, there are no firm criteria for what is an acceptable group. . . . The characteristics and source of the case series must heavily influence the type of control selected if comparability of the two series is to be achieved, that is, if selection bias is to be avoided." The source of controls is shown in Table 5-3. Entries under "Controls" in Table 5-14A may have questionable comparability of cases and controls or just not be matched by design on any variables (see individual studies in Appendix A). In numerous studies, the data for ETS subjects were drawn from a larger study that includes active smokers and was usually matched on several variables (Table 5-3). If smoking habit was not a matching variable, however, then the ETS data alone are not matched (indicated under "ETS sample matched" in Table 5-3). Matching is a way of equalizing confounding variables, although they still should be taken into account in the analysis. When matching is not implemented, then confounding variables can only be controlled for in the analysis.

In Table 5-14A, "Representativeness" refers to whether the ETS subjects are reasonably representative of the target population, which is the general public for purposes of this report. Lack of representativeness is not always a negative characteristic, but it needs to be taken into account. The implications are usually more relevant for characterizing population risk than for hazard identification.

The headings under "Collection" in Table 5-14B are more self-explanatory. It is noted in the table whether a "Self-Questionnaire" was used, which may be a source of bias of undetermined direction. Among the studies under "Response and Follow-up," two (GENG and KATA) provide no information. Good follow-up is essential to cohort studies, as indicated in the notes above. Follow-up is lacking in some respect in three of the four cohort studies, all of which are in westernized countries, although GARF(Coh) is the only large one. The direction of potential bias is not evident.

"Proxy Response" in Table 5-14B identifies studies where information from surrogate respondents, typically, next-of-kin, was used, as necessary, or no information was provided. Subject response is generally considered more reliable than proxy response. Proxy response percentages are shown for cases and controls in Table 5-3. The results of GARF might suggest upward bias; those of JANE, downward. In JANE, type of respondent is a matching variable, and

250103188S

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

controls are "healthy." In GARF, by contrast, proxy responses are from cases only (889 of cases), and the controls are cancer patients themselves. Unfortunately, it is not clear what factors may affect bias from proxy response, which direction the bias may take, or how serious it may be.

The "Analysis" classification in Table 5-14B refers to methods of data analysis. How were unmarried women treated with regard to exposure to ETS, where the "Unmarrieds" heading refers to women who are not currently married or have not been continuously married to the same husband for an extended period? Studies vary in the degree to which exposure history is taken into account, and some introduce assumptions regarding exposure of women who have never been married (e.g., equivalent to being married but not exposed to ETS). A study is listed under "Unmarrieds" if information is lacking or if unmarrieds are included with assumptions regarding exposure. In several instances both apply or some information is lacking (e.g., LAMT treats single women as unexposed to ETS, but it is not clear how exposure was handled for widows and divorcees; 60 of the subjects in KOO are widows, but their distribution between cases and controls is unknown). The "Unmarrieds" topic is closely related to the "ETS Subjects" and "ETS Exposure" subheadings under "Classification" in Table 5-14A. The direction of bias need not be consistent across entries in this category.

An adjusted analysis takes into account potential confounders. In particular, variables that have been used for matching in the design should be incorporated in the analysis as potentially confounding variables. This follows because the matching factors must be considered a priori as ones for which stratification would be necessary, that is, as confounding variables (Breslow and Day, 1980). We would expect matching on age, at least. Because the ETS data alone are not matched on any variable in many studies (Table 5-3), a form of analysis that adjusts for potential confounding appears particularly relevant. For the studies with both a crude and adjusted analysis (Table 5-5), the adjustments have only a small to moderate effect in either direction. A study is included under "Adjusted Analysis" in Table 5-14B if no adjusted analysis was conducted or if we had a problem with the method used (details are in Appendix A). The three entries under "Trend Analysis" in Table 5-14B are listed because the outcomes are of questionable interest, either due to small sample size or because of the method or interpretation of data analysis.

It is concluded from the above discussion that there are no additional sources of bias (other than smoker misclassification, which was adjusted for in Section 5.2) that would systematically cause higher observed relative risk estimates. Therefore, this report concludes that the observed association between ETS and lung cancer cannot be explained by bias. In fact, the association is

2501031886

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

apparent despite the existence of the downward bias that results from nearly universal ETS exposure, which has not yet been corrected for.

5.4.4. Potential Effects on Individual Studies

This section compares the utility of individual studies for determination whether there is an association between ETS and lung cancer. For selected studies in Table 5-11, largely those with power greater than 0.20, principal characteristics related to potential bias and confounding are discussed. For studies with a significant outcome, indicated by boldface type in Table 5-11, attention is focused on influences that would cause the relative risk to be overstated; otherwise, influences toward unity are of greater interest. Independent of the quantitative results, the utility of a few studies for ETS is questionable because of limited information, low quality, or inadequate control for other (non-ETS) household risks of lung cancer (most prominently, indoor smoke). The tier number assigned to a study on the basis of the critical analysis in Appendix A is presented at the end of each discussion.

AKIB

Extensive use of proxy respondents (Table 5-3) and poor response rate may have led to poor quality of exposure data and/or selective response. These could have contributed to the observed association between spousal smoking and lung cancer if (1) proxies of lung cancer cases were more inclined to "remember" a history of spousal smoking than were those of controls or (2) persons suspecting an ETS-lung cancer link were more likely to participate in the study. The possible lack of subject-interviewee blinding potentiates both possibilities. With regard to (1), however, type of informant was reported to have no significant effect on the results, and the *typical* influence of poor exposure data is in the direction of no effect. ETS subjects are atomic bomb survivors (Table 5-3), which affects representativeness but not hazard identification, to our awareness. Finally, reliance on diagnoses based only on radiological or clinical evidence in nearly one-half (43%) of the cases (Table 5-15) could have led to substantial misclassification of disease status, probably creating a bias toward the null. (Tier 2)

CHAN

A number of factors may have had a bearing on the nonsignificant negative association this study observed between ETS exposure at home or work and lung cancer. The measure of ETS exposure utilized is nonspecific and subjective, lumping together home, work, childhood, and

05/15/92
2501031887

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

adulthood exposure, which is determined primarily by adult at-home exposure. No histological or cytological diagnosis was performed in 18% of cases, and there is no indication that secondary tumors were excluded (Table 5-15). These characteristics contribute to potential error in disease or exposure classification, both sources of downward bias. Orthopedic-ward controls may not have been appropriate or comparable to cases, particularly insofar as the total control population appeared to contain an elevated proportion of smokers compared to the general population in the area; they might thus be more ETS exposed as well, thereby producing a negative bias. Treatment of unmarrieds is unknown, and nearly one-half of the eligible cases were not included, raising the possibility of selection bias; the probable direction of effect of these factors is unknown. Finally, only a crude analysis is presented. Although cooking fuel, residence, and occupation did not appear significantly associated with lung cancer, no attempts were made to control for potential confounders. The uncertainty due to potential confounding, bias, and inadequate statistical methods, along with neglect of basic epidemiologic principles needed for credibility, render this study of little value for evaluation of ETS and lung cancer. (Tier 4)

CORR

Several potential biasing factors need to be considered with regard to the positive (but not statistically significant) association between ETS and lung cancer noted in this study. The comparability of cases and controls is uncertain; for the most part, the direction of effect of this noncomparability of cases and controls is equally uncertain, but the fact that 15% of the controls had cardiovascular disease would presumably lead to some *downward* bias in association. Not considering former smoking status or duration of exposure in some spousal smoking analyses is conducive to exposure misclassification, with consequent upward and downward bias, respectively. Proxies were used more frequently for cases (24%) than for controls (11%), at least in the parent study (Table 5-3), but exclusion of proxy respondents was reported to have no effect on the results for spousal smoking. Treatment of widows and divorcees is unclear, and misclassification of these women as "unexposed" despite smoking by former husbands, *if* it occurred, could bias downward. More substantial potential to distort the results is presented by an inadequate approach to confounding. While stratification on race or respondent type reportedly had no effect on results, a dichotomization into women over and under 60 years of age was the only attempt to control for age or other factors. This marginal control for age and lack of control for socioeconomic status (SES) and other potential confounders leaves open the possibility that

250103188

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

such factors may have significantly contributed to the observed association--either positively or negatively. (Tier 3)

FONT

The positive associations between four separate sources of adult ETS exposure and lung cancer, all of which reach statistical significance when restricted to adenocarcinoma, cannot be readily explained by bias and confounding. This study was designed to investigate the ETS-lung cancer relationship specifically and goes to great lengths to minimize potential bias and confounding. Reliance on proxies for some subjects' exposure information apparently introduced no problem, because exclusion of proxy responses reportedly did not alter the results. ETS subjects may have smoked up to 6 months, however, and if that amount of smoking has an affect on lung cancer risk, it could be a source of mild upward bias, depending on the number of subjects with smoking histories. Diet, cooking and heating practices, and occupation were not directly controlled for (such analyses are pending in an expanded version of this study), leaving open the potential for confounding with either upward or downward effects. These factors, however, might well co-vary with age, race, geographic area, income, and education, and results were adjusted for this combination of variables (Table 5-5). In addition, adjusted results were virtually independent of whether colon cancer or general population controls were used, providing general evidence against selection or recall bias (Table 5-5). And although it remains possible that lung cancer cases and their proxies tended to overestimate their ETS exposure relative to colon cancer patients, it is unlikely that such recall bias would be specific to adenocarcinoma. (Tier 1)

GAO

The small nonsignificant association of lung cancer incidence with spousal smoking, and the lack of association with total ETS exposure, may have been influenced by several factors. First, only duration (not intensity of ETS exposure) was considered, and spousal exposure of less than 20 years' duration was disregarded. Substantial misclassification of exposure is likely, a source of downward bias. Second, ETS controls and cases were unmatched and their comparability is unclear; the controls in the combined ETS and non-ETS population contained a higher proportion of individuals in the oldest age group than did the cases, but analyses were adjusted for age. Third, 19% of these cases were diagnosed solely by radiological or clinical means (Table 5-15), increasing the likelihood of disease misclassification and the attendant bias toward the null. Finally, spousal smoking (though not all-source ETS) analyses were also

2501031889

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

adjusted for education, but there was no adjustment or other control for a number of variables (e.g., several cooking habits and previous respiratory diseases) found to be significantly and/or more strongly associated than ETS with lung cancer in the data. Confounding by such factors could have biased results in either direction. Thus, results were probably biased downward by exposure classification problems and possibly also affected in unknown degrees by apparent non-ETS risk factors. (Tier 3)

GARF

The main drawback of this study lies in its heavy reliance on proxy respondents (88% of cases, unknown percentage of controls--Table 5-3). The statistically significant association between high ETS exposure from spouse or related cohabitant and lung cancer disappears when proxy respondents are excluded, but it is unclear whether this is the result of eliminating upward bias operating among proxy respondents or simply a random consequence of eliminating most of the study population. A systematic recall bias among proxy respondents is less likely given the reported blinding of interviewers and subjects to the study hypothesis and the use of colorectal cancer controls. Confounding due to dietary, heating, or cooking practices was not assessed and thus could potentially have produced bias in either direction, but it is unclear why such bias would have operated selectively on cases where offspring rather than patients themselves were interviewed. (Tier 2)

GARF(Coh)

Although an unusually large study with good power, this cohort investigation suffers from a number of limitations that in aggregate greatly mitigate its ability to detect a putative ETS-lung cancer association and could account for its lack of significant findings. Data on exposure are limited to husband's self-reported current smoking habits in 1959, and no information on former spouses or other ETS sources was collected. Tremendous potential for distortion and misclassification of relevant ETS exposure thus exists, providing a likely bias toward the null hypothesis (it is possible that wives of smokers had a greater tendency to become active smokers during follow-up, thus producing an increase in risk of lung cancer, but the authors state that change in smoking status during follow-up was rare, so this effect, if extant, should be minor). In addition, diagnostic confirmation and exclusion of secondary lung cancers was carried out for less than one-third of the cases (the actual percentage was not stated), creating opportunities for disease misclassification and another likely resultant bias toward the null. These and other factors

250103890

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

(see review in Appendix A) could have reduced the observed association--which approached statistical significance--below the nominal significance level and/or distorted the dose-response pattern. (Tier 3)

GENG

The positive and statistically significant association, complete with clear dose-response pattern, between spousal smoking and lung cancer is difficult to assess due to the dearth of details supplied in the short published report. It is not clear that former personal smoking habits were considered, for example, presenting a potential for upward bias arising from an association of former smoking with spousal smoke exposure. Information on comparability of cases and controls, response rates, utilization of proxies, and treatment of martial status are lacking, precluding evaluation of these potential sources of error. No potential confounding factors are taken into account, despite the observation of substantial associations between several non-ETS exposures and lung cancer. Given the lack of design and methodological detail and absence of efforts to address confounding, the influence of bias and confounding cannot be assessed beyond noting that it may be substantial. (Tier 4)

HIRA(Coh)

The statistically significant positive association and trend for lung cancer with spousal smoking and some other ETS exposures observed in the HIRA study cannot readily be explained by bias or confounding. Classification based on self-reported status at baseline interview, without regard to possible changes in status over time, could cause the RR to be overstated, but the bias (expected effect) is in the other direction for error in exposure measurement. The use of death certificates, with potential inaccuracies leading to misclassification of primary lung cancer, is also a source of downward bias. The age adjustment is handled poorly in the analysis of cohort data, utilizing the husband's rather than the subject's age, but that is corrected in the nested case-control analyses, with similar results. More sophisticated methods of survival analysis could be implemented, but that is unlikely to affect the evidence significantly.

Related observations of interest include the following: increased emphysema, asthma, and paranasal sinus cancer in women exposed to spousal smoking. Among consumption of foods (green-yellow vegetables, fish, meat, milk, and soybean paste soup), meat consumption is more common among wives of smoking husbands. Consumption of fish is associated with higher lung cancer incidence; meat consumption is suggestively associated with lower incidence. The analysis

250103189

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

for dietary habits controls for wife's age and husband's occupation but not for possible confounding between food types. (Tier 2)

INOU

The odds ratio of 2.55 is quite high, even for Japan, and is based on a relatively small number of subjects. Unfortunately, the sparse details provided regarding the study's design and execution make assessment nearly impossible. For example, no data are provided on means of diagnosis or confirmation, if any, and there is no indication that secondary cancers were excluded (Table 5-15); reliance on proxy respondents may have reached 100% (Table 5-3), and there is no indication of blinding or consideration of former (versus current) smoking status. These and other potential problems could have substantially biased the results upward--or downward. The high uncertainty associated with this study, in part due to very limited information about it, renders it potentially misleading to the point that it may be preferable to omit it from the analysis. (Tier 4)

JANE

The results of this large and largely well-executed study are enigmatic. Overall, spousal smoking is not positively associated with lung cancer, whereas all-cohabitant smoking is somewhat associated and childhood smoking is substantially associated. Yet when observation is limited to those subjects with at least some exposure, estimated lung cancer risk increases with increasing exposure; further, while proxy respondents yield substantially *negative* overall spousal smoking-lung cancer associations, nonproxies yield consistently more positive results. Confounding by smoking habits of other cohabitants could have decreased the association seen for spousal smoking. The study's treatment of unmarrieds is unknown and thus theoretically could have affected results, such effects usually being a downward bias through exposure misclassification. Supporting that possibility is the high prevalence of exposed controls (80%), suggesting that the requirement for classification as ETS-exposed may be too lenient, a source of downward bias. That aside, the only glaring flaw in the study's conduct is the pooling of male and female subjects, with no consideration of gender in the analyses. It is clear that this could lead to a weaker observed association than analyses restricted to females if smoking by the spouse is generally more intense and/or contributes a greater proportion of total ETS exposure for women than for men, as seems likely. But it is unclear why this would drive the risk estimates for spousal smoking, but not for exposure from all-cohabitant or childhood ETS, below unity or produce the observed

250103892

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

response curve. Several speculative mechanisms are suggested in the more extensive study review (see Appendix A), but the study's results cannot be clearly attributed to a negative bias. (Tier 2)

KALA

Interviewer bias is the only obvious potential "flaw" in this high-quality study that could have substantially contributed to the observed positive association between spousal smoking and lung cancer. Adjustment for interviewer, however, along with age and education (Table 5-5) strengthened the observed association (unadjusted OR = 1.60, adjusted OR = 1.92), arguing against interviewer bias as the source of the results.

Related observations of interest pertain to analyses evaluating 16 food groups. Consumption of fruit appears to have a protective effect; retinol is marginal; no effect was found for β-carotene. (Tier 1)

KOO

This study's analyses of various measures of ETS exposure yielded predominantly positive but uniformly nonsignificant associations with lung cancer. The study's modest sample size--and hence modest power (0.43)--could have contributed to the failure to achieve statistical significance, but other factors may have influenced the results as well. The complexity and assumptions of several of the approaches used to quantify exposure are questionable (e.g., simultaneous exposures were not added and lifetime average exposure was estimated by dividing current exposure level by age). Such approaches may have increased misclassification, probably with a bias toward the null, and in combination with small numbers within exposure strata may have contributed to the downward dose-response pattern over the range of ETS exposure (the dose-response patterns observed appeared to be sensitive to the measure of exposure used). Comparability of the cases and controls utilized in the ETS analyses is uncertain (unmatched; no demographics), so bias in either direction is possible. A number of potential confounders were included in the analyses (e.g., age, place of residence, public versus private housing), so significant confounding by standard age or SES-related factors is unlikely. There were no data available on diet or cooking habits that have shown evidence of substantial though inconsistent associations with lung cancer in some other studies conducted in Hong Kong. Bias in any direction could potentially have arisen from this source, but adjustment for age, education, and residence--factors probably co-varying to some degree with diet and cooking habits--resulted in

2501031893

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

stronger ETS-lung cancer associations, thus hinting that potential confounding by diet or cooking would probably introduce a downward bias, if any. (Tier 2)

LAMT

Assessment of the statistically significant positive association between spousal smoke exposure and lung cancer observed in this study includes several potential sources of bias and confounding. Although cases and controls appeared highly comparable as initially assembled, they were not matched on smoking, and thus the nonsmokers used in the ETS analysis may not have been as comparable, leading to potential bias of indeterminate direction. While exclusion of single women reportedly did not alter results, treatment of widows and divorcees was unclear and thus could have potentially led to exposure misclassification and another indeterminate bias. Finally, and most important, no attempt to control for major potential confounders, including the fundamental factor of age, was undertaken (except for the gender restriction). Often, adjustment for such factors has little effect on results, but such an outcome cannot simply be assumed, and thus the potential for significant upward (or downward) shifts in association due to confounding exists. (Tier 2)

LAMW

Despite only modest power (0.39), this study found a statistically significant association between ETS exposure and lung cancer. Comparability of cases and controls is unclear because the ETS population was unmatched and not demographically characterized, leaving bias of indeterminate direction. Similarly unpredictable but potentially more important is the effect of possible confounding factors that were not addressed in the analyses. Neither kerosene fume nor incense exposure was significantly associated with lung cancer, but no other potential confounders--including age--were investigated. Thus, strong effects in either direction due to confounding by basic risk factors cannot be ruled out, although the potential effects of other possible sources of bias are preponderantly negative. (Tier 3)

LIU

The small but not statistically significant negative association between passive smoking and lung cancer observed may have been shaped by bias and confounding. Uncertain case-control comparability, scarcity of histopathological diagnosis, lack of diagnostic verification and exclusion of secondary tumors (Table 5-15), and a nonspecific and nonquantitative ETS measure probably

2501031894

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

reduce accuracy of disease and exposure assessment and bias results toward the null. Lack of control for nearly all relevant potential confounders could distort the observed association in any direction. The ubiquitous exposure to smokey coal combustion products, which often reaches extreme levels in the study area, makes evaluation of a comparatively minor exposure like ETS particularly problematic--even for *active* smoking, only a weak association of ever-versus never-smoking with lung cancer is detected. Due to these problems, this study's findings regarding ETS are not very meaningful. (Tier 4)

PERS

It appears likely that the potential sources of upward bias actually have little effect, leaving several possible sources of downward bias. Although data on smoking status in 1963-64 were collected directly from subjects, data on ETS were derived from follow-up questionnaires distributed in 1984. Because only cases diagnosed by 1980 were included in the study, proxy respondents must have been used for most lung cancer cases, although no actual numbers are supplied. The nearly identical results obtained for controls matched on vital status (and hence requiring proxy respondents) and for nonstatus-matched controls indicate that a systematic bias in responses of proxies versus nonproxies was not responsible for the observed results. Preferential recall of ETS exposure by relatives of lung cancer cases remains a possibility, particularly as controls were drawn from the general population. Observed associations were specific for squamous and small cell cancer only, however, while recall bias would be expected to affect all lung cancer types equally. Assessment of exposure was compromised by basing spousal exposure of remarried women on only their longest marriage and classifying all unmarried women as unexposed, sources of downward bias. Reliance on self-administered questionnaires may also reduce data accuracy, also a downward bias. It is reported that occupation, radon exposure, and urban location were not important factors. (Tier 2)

SHIM

Downward bias may be a factor. The inconsistent although largely positive associations noted between various sources of ETS exposure and lung cancer in this study may have been affected by several sources of bias and confounding. Lack of consideration of tobacco products other than cigarettes, no differentiation between past and current exposures, and an unstated (and thus possibly imprecise) definition of exposure may have led to misclassification of exposure status and consequent downward bias. Failure to exclude smoking-related diseases from the

250103189

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

hospital control group and use of a self-administered questionnaire may also contribute to downward bias. There was no control for age or other potential confounders such as marital status, nor for occupational metal exposure, heating fuel type, or medical history of silicosis, despite observation of substantial though not statistically significant associations of these factors with lung cancer. The direction of bias possibly introduced by these uncontrolled factors cannot be determined.

Results of related interest include the findings that occupational exposure to iron or other metals is significantly associated with lung cancer (OR = 4.8); for exposure to coal, stone, cement, asbestos, or ceramics, the OR is 3.3, but it is not statistically significant. No effect was found for the eight food groups evaluated. A personal medical history of silicosis is suggestive (OR = 2); a history of chronic bronchitis, asthma, or tuberculosis is not. Recent use of a kerosene or coal (charcoal) stove for household heating may be of interest (OR = 1.6 and 1.7, respectively). It is clear that some variables were adjusted for others, in particular, the group classifications of sources of ETS in the home. With so many potential non-ETS factors addressed, however, it would appear unlikely that all possible confounders could be controlled. (Tier 3)

SOBU

Upward bias or confounding stemming from the sources of uncertainty in this study are a possibility. Cases and controls are unmatched, with apparent differences that may affect comparability. Controls tend to be younger and more educated--variables that are taken into account by an adjusted analysis. Education and age, however, may reflect differences in lifestyle and socioeconomic status that could be biasing. In this study, exposure from spousal smoking alone is analyzed separately from smoking only from other cohabitants, with the latter significant and the former nonsignificant (see Table 5-5; the results for the latter appear in Table 5-11). It is possible that the higher OR for smoking cohabitants could be confounded by some factor related to lifestyle, although it is not clear how. The results for ETS need to be adjusted for use of wood and straw as cooking materials, a possible risk factor for lung cancer (OR = 1.9). Possible inaccuracies in exposure and other risk factor assessments resulting from use of a self-administered questionnaire are further features that may have compromised results. That might increase nondifferential misclassification, however, biasing the relative risk toward unity.

Related observations of interest include the following: significant association with lung cancer for women who had used wood or straw as cooking fuels at age 30 (OR = 1.9). Other

250103189 6

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

sources of indoor heating (by gas, kerosene, coal, charcoal, and wood stoves without chimneys) were not significant nor was the use of charcoal foot warmers. (Tier 3)

SVEN

The small size of the nonsmoking female population in this study leads to nonsignificant results even for the OR of 2.1 observed for women exposed to ETS both at home and at work. The OR for exposure at home or work, but not both, is only 1.2. These results could thus be attributed to chance, but the dose-response pattern argues against this interpretation. The nonquantitative and rather rough measures of exposure used would most likely have lessened the observed association rather than biasing the ORs upward. All interviews with cases were face to face, but 42% of the controls were interviewed by telephone. If persons interviewed by telephone were less likely to report or recall ETS exposure than those interviewed face to face, this could explain the observed association. The researchers report that results were similar regardless of whether hospital or general population controls were used, however, and presumably the telephone interviews were predominantly those for general population controls. Although treatment of unmarried subjects is not mentioned, bias toward the null due to exposure misclassification from this source is unlikely because no analyses limited to spousal exposure were conducted. (Tier 2)

TRIC

The statistically significant positive association between spousal smoking and lung cancer observed in this study is not readily attributable to general sources of bias and confounding. The inclusion of smokers who quit over 20 years before the study tends to bias results toward no association, unless occurrence of a strong correlation between such former smoking and having a smoking spouse contributed an upward bias. The frequency of diagnoses based only on radiological and/or clinical means, coupled with lack of diagnostic confirmation or exclusion of secondary tumors (Table 5-15), potentiates disease misclassification and thereby bias toward the null. Possible lack of blinding could have led to some (upward) interviewer bias. And while standard demographic factors associated with lung cancer were not associated with spousal smoking, diet and cooking and heating practices were not specifically addressed, leaving some potential for confounding (either positive or negative) by these factors. A constellation of positive biases sufficient to offset their negative counterparts and produce associations of the magnitude (e.g., ORs in excess of 2) observed, however, seems unlikely. (Tier 2)

250103187

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

WU

This study found several nonsignificant positive associations between ETS exposure and lung cancer. Cases were restricted to adenocarcinoma and squamous cell carcinoma, but because these are the predominant cell types anyway, it should not have significantly compromised the results. Most analyses employed adjustment for personal smoking habits within a population of smokers and nonsmokers; comparability of cases and controls within this population appeared excellent. The comparability of *nonsmoking* cases and controls is unclear; a lack of comparability in key areas (e.g., age) could have influenced results. Both smoking-adjusted and never-smoker-restricted approaches yielded positive associations, however. A very high proportion (44%) of identified cases were not included in the study, but this was largely due to avoidance of proxy respondents. Excluded cases were demographically similar to those included, arguing against a selection bias. Handling of former marriages was not described, leaving open a possibility for upward or downward bias from this source. The matched-pairs analysis by its nature eliminated the possibility of confounding due to age or neighborhood. Because the analysis attempted to adjust for the effect of active smokers, instead of removing the data on active smokers, isolation of the effects of ETS on lung cancer from those of personal smoking habits is subject to question. An analysis restricted to nonsmokers was unmatched and thus subject to potential confounding by age and/or neighborhood. Both approaches produced similar results, however, making such confounding less likely.

More problematic is the failure to control for dairy product and egg intake despite its substantial association with lung cancer. The nature of the connection (if any) between this factor and ETS exposure, and hence the magnitude and direction of bias it would introduce, is not clear. No clear attribution of the results to any of the above sources is possible, because their potential effects could have been in any direction. In analyses of non-ETS factors, childhood pneumonia is significantly associated with lung cancer (only cases of adenocarcinoma and squamous cell carcinoma were included in the study), but history of six other lung diseases were not. Also significant is heating or cooking with coal during the preadult years and diets low in β-carotene, dairy products, or eggs. No significant associations were noted for vitamin A intake or for occupation. (Note: It is clear that some variables were adjusted for others, but with so many potential non-ETS factors addressed, it would appear unlikely that all possible confounders could be controlled. Multiple comparisons may cause some results to appear more significant than warranted.) (Tier 2)

2501031898

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

WUWI

Despite excellent power, this study found a slightly negative association between ETS exposure and lung cancer. Classification of subjects with histories of up to 6 months of active smoking as never-smokers may be a source of upward bias, while the lack of histological diagnosis for 26% of the cases (Table 5-15) may have increased disease misclassification, a source of downward bias. Controls were rather loosely matched (and only on age) to cases, so comparability could have been a problem of indeterminate direction of effect. This potential is mitigated by adjustment for age, education, and area in the analyses, which also largely controls for confounding by key demographic-associated factors. The factor that makes this study of little value for ETS exposure, however, is the presence of other household factors found to be substantially associated with lung cancer, indoor smoke from nontobacco sources in particular. If ETS is a risk factor for lung cancer, its relative risk is reasonably small and unlikely to be detected against a background of competing and probably stronger exposures (e.g., indoor coal combustion products). The authors note the limitation of their exploratory study for inference on ETS and lung cancer: "Perhaps in this study population the effect of environmental tobacco smoke was obscured by the rather heavy exposures to pollutants from coal-burning Kang, other indoor heating sources, and high levels of neighborhood air pollution." Although it is informative vis-a-vis its principal objectives, this study is not very useful for assessing ETS exposure and lung cancer. (Tier 4)

5.4.5. Analysis by Tier and Country

The assignment of studies to tiers is summarized in Table 5-16. Tier 1 contains the studies judged to be of highest utility for addressing the potential relationship of ETS and lung cancer, based on the material in the last sections and the detailed reviews in Appendix A. Overall, only three studies are in the highest tier, while 12, 10, and 3 studies are in Tiers 2, 3, and 4, respectively. Studies in Tier 4 are not recommended for the reasons described in the previous section. The statistical weight for Tiers 1 and 2 pooled together for each country is shown in Table 5-17 as a percentage of the total for corresponding tiers over all countries, except for China where the weight for Tier 3 is used in the absence of studies in Tiers 1 and 2. Emphasis on studies through Tier 2 is somewhat arbitrary--aside from the United States, the power of Tier 1 alone is too small. GAO is the only study in China that was not placed in Tier 4, but there is little basis to assume that this single study from Shanghai should be "representative" of a vast country like China.

2501031899

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-17 presents adjusted relative risk estimates, 90% confidence intervals, and significance levels (one-sided) from studies pooled by country and by tier. The results of using only the higher utility studies (Tier 1 and Tier 2) are generally similar to those generated by using all studies, with the higher ranked studies yielding slightly higher estimates of relative risk for five of the six country groups. The pooled estimates from the higher utility studies are all greater than one and are statistically significant for four of the five higher tiered (Tiers 1 and 2) country groups--Greece, Hong Kong, Japan, and the United States, in that order. The pooled results from the three Western European Tier 1 and 2 studies show about the same association as those of the six U.S. studies but, with less power, are not statistically significant.

Analysis by tiers provides a methodology for weighing studies both qualitatively and quantitatively. Qualitatively, it allows one to emphasize the better designed and conducted studies, thought to provide better data for analysis of an ETS effect. The addition of studies of lower utility to the analysis, however, has only a small effect. In view of that outcome, and the results and discussion in Sections 5.4.2 and 5.4.3, this analysis indicates that confounding and bias in these studies have little effect on the overall results. In summary, it is concluded that the association of ETS and lung cancer observed from the analysis of the 31 epidemiology studies in eight different countries is not due to chance alone and is not attributable to bias or confounding.

5.5. CONCLUSIONS FOR HAZARD IDENTIFICATION

5.5.1. Criteria for Causality

According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The *Guidelines* establish "three criteria (that) must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

As indicated in Section 5.3, the overall results observed in the 31 epidemiology studies are highly unlikely to be due to chance. The discussion and analyses in Section 5.4 conclude that the association cannot be explained by bias or confounding either.

05/15/92
250103190O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

In addition, the evidence for a causal association between ETS and lung cancer is evaluated according to seven specific criteria for causality developed by an EPA workshop to supplement the *Guidelines* (U.S. EPA, 1989). These criteria are similar to the original and classical recommendations of Hill (1953, 1965). The seven recommended (but not official) criteria from the EPA workshop, which vary between essential and desirable, are listed below (U.S. EPA, 1989).

> A causal interpretation is enhanced for studies to the extent that they meet the criteria described below. None of these actually establishes causality; actual proof is rarely attainable when dealing with environmental carcinogens. The absence of any one or even several of the others does not prevent a causal interpretation. Only the first criterion (temporal relationship) is essential to a causal relationship: with that exception, none of the criteria should be considered as either necessary or sufficient in itself. The first six criteria apply to an individual study. The last criterion (coherence) applies to a consideration of all evidence in the entire body of knowledge.

1. Temporal relationship: The disease occurs within a biologically reasonable time frame after the initial exposure to account for the specific health effect.

2. Consistency: When compared to several independent studies of a similar exposure in different populations, the study in question demonstrates a similar association which persists despite differing circumstances. This usually constitutes strong evidence for a causal interpretation (assuming the same bias or confounding is not also duplicated across studies).

3. Strength of association: The greater the estimate of risk and the more precise, the more credible the causal association.

4. Dose-response or biologic gradient: An increase in the measure of effect is correlated positively with an increase in the exposure or estimated dose. If present, this characteristic should be weighted heavily in considering causality. However, the absence of a dose-response relationship should not be construed by itself as evidence of a lack of a causal relationship.

5. Specificity of the association: In the study in question, if a single exposure is associated with an excess risk of one or more cancers also found in other studies, it increases the likelihood of a causal interpretation.

6. Biological plausibility: The association makes sense in terms of biological knowledge. Information from toxicology, pharmacokinetics, genotoxicity, and in vitro studies should be considered.

7. Coherence: Coherence exists when a cause-and-effect interpretation is in logical agreement with what is known about the natural history and biology of the disease. A proposed association that conflicted with existing knowledge would have to be examined with particular care. (This criterion has been called "collateral evidence" previously.)

25010319 01

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

5.5.2. Assessment of Causality

We consider the extent to which the criteria for causality are satisfied for the ETS studies. Regarding *temporal relationship*, ETS exposure classification is typically based on the marital history of a subject, which varies, or on the status at the beginning of a prospective cohort study. There are seven exceptions where exposure classification is based only on current status or duration of exposure appears not to have been taken into account (see reviews of studies entered under "ETS Exposure" in Table 5-14). None of the seven (BUFF, CHAN, GAO, INOU, KABA, LEE, and SHIM) are in Tier 1 or 2. This criterion appears to be adequately satisfied for the studies in Tiers 1 and 2.

If ETS causes lung cancer, then the true relative risk is small for detection by epidemiologic standards and may differ between countries as well. However, by considering the totality of the evidence, it is determined that the large accumulation of epidemiologic evidence from independent sources in different locales and circumstances, under actual exposure conditions, is adequate for conclusiveness. Having accounted for variable study size, adjusted for a possible systematic spousal bias due to smoker misclassification, and considered potential bias, confounding, and other sources of uncertainty on a study-by-study basis, *consistency* of a significant association is clearly evident for the summary statistical measures for Tiers 1 and 2 in Greece, Japan, Hong Kong, and the United States. The combined countries from Western Europe are similar in outcome for the United States, although significance is not attained. There is too much obscurity and uncertainty attached to the studies in China for adequate data interpretation.

The relative risks for each country are obtained by pooling estimates from the epidemiologic studies conducted in the country. The *strength of observation* is limited by the true value of the relative risk, which is small. Statistical significance is attained, however, for the pooled studies of the United States and most other countries. The data were obtained from actual conditions of environmental exposure so imprecision is not increased by extrapolation of results from atypically high exposure concentrations, a common situation in risk analysis. Additionally, all studies were individually corrected for systematic bias from smoker misclassification at the outset, and qualitative characteristics of the studies were carefully reviewed to emphasize the results from the better studies. The outcome for the United States is heavily influenced by the large NCI study (FONT) that was specifically designed and executed to avoid methodologic problems that might undermine the accuracy or precision of the results.

Of the 14 studies reporting test for upward trend, 8 are statistically significant at 0.05 (nine at 0.06). The outcome is similar for studies in Tiers 1 and 2 only--6 of 10 are significant,

250103190?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

which would occur by chance alone with probability less than 0.0001. In four of those six significant studies, the observed RR values increase monotonically with dose (i.e., the RR increases with each increase in exposure level). This evidence of *dose-response* is very supportive of a causal interpretation because it would be an unlikely result of any operative sources of bias or confounding.

Specificity does not apply to ETS. Although ETS has been assessed for the same endpoint (lung cancer) in all studies, the occurrence of lung cancer is not specific to ETS exposure. Data on histological cell type are not conclusive. The study by Fontham and colleagues (1991) suggests that adenocarcinoma may be more strongly related to ETS exposure than other cell types. Adenocarcinoma, however, does not appear to be etiologically specific to ETS.

Biomarkers such as cotinine/creatinine levels clearly indicate that ETS is taken up by the lungs of nonsmokers (see Chapter 3). The similarity of carcinogens identified in sidestream and mainstream smoke, along with the established causal relationship between lung cancer and smoking in humans with high relative risks and dose-response relationships in four different lung cell types down to low exposure levels, provide *biological plausibility* that ETS is also a lung carcinogen (Chapter 4). In addition, animal models and genotoxicity assays provide corroborating evidence for the carcinogenic potential of ETS (Chapter 4). The epidemiologic data provide independent empirical verification of the anticipated risk of lung cancer from passive smoking and also an estimate of the increased risk of lung cancer to never-smoking women. The *coherence* of results from these three approaches and the lack of significant arguments to the contrary strongly support causality as an explanation of the observed association between ETS exposure and lung cancer.

5.5.3. Conclusion for Hazard Identification

Based on the assessment of all the evidence considered in Chapters 3, 4, and 5 of this report and in accordance with the EPA *Guidelines* and the causality criteria above for interpretation of human data, this report concludes that ETS is a Group A human carcinogen, the EPA classification "used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer" (U.S. EPA, 1986a).

250103 1903 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-1. Epidemiologic studies on ETS and lung cancer in this report

Study[1]	Country	Within country	References
$AKIB_2$	Japan	Hiroshima	Akiba et al. (1986)
$BROW_3$	USA	Colorado	Brownson et al. (1987)
$BUFF_3$	USA	Texas	Buffler et al. (1984)
$CHAN_4$	Hong Kong		Chan and Fung (1982)
$CORR_3$	USA	Louisiana	Correa et al. (1983)
$FONT_1$	USA	Five metro areas	Fontham et al. (1991)
GAO_3	China	Shanghai	Gao et al. (1987)
$GARF_2$	USA	New Jersey, Ohio	Garfinkel et al. (1985)
$GENG_4$	China	Tianjin	Geng et al. (1988)
$HUMB_2$	USA	New Mexico	Humble et al. (1987)
$INOU_4$	Japan	Kanajawa	Inoue and Hirayama (1988)
$JANE_2$	USA	New York	Janerich et al. (1990)
$KABA_2$	USA	New York	Kabat and Wynder (1984)
$KALA_1$	Greece	Athens	Kalandidi et al. (1991)
KATA[2]	Japan		Katada et al. (1988)
KOO_2	Hong Kong		Koo et al. (1987)
$LAMT_2$	Hong Kong		Lam et al. (1987)
$LAMW_3$	Hong Kong		Lam (1985)
LEE_3	England		Lee et al. (1986)
LIU_4	China	Xuanwei	Liu et al. (1991)
$PERS_2$	Sweden		Pershagen et al. (1987)
$SHIM_2$	Japan	Nagoya	Shimizu et al. (1988)

25010319 04

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-1. (continued)

Study[1]	Country	Within country	References
$SOBU_3$	Japan	Osaka	Sobue (1990)
WU_2	USA	California	Wu et al. (1985)
$WUWI_4$	China		Wu-Williams and Samet (1990)
$BUTL(Coh)_2$	USA	California	Butler (1988)
$GARF(Coh)_3$	USA		Garfinkel (1981)
$HIRA(Coh)_2$	Japan		Hirayama (1984)
$HOLE(Coh)_1$	Scotland	Paisley Renfrew	Hole et al. (1989)

[1] Subscripts refer to this report's ratings of studies for utility of studying the association of ETS and lung cancer, where "1" is highest. Studies with "4" are judged to be of little value. The ratings are subjective, based on qualitative features described in the reviews (Appendix A). It was not possible to describe meaningful rule to follow in setting a rating. Nevertheless, it is useful to have some indication of which studies have taken greater care to avoid or control for potential bias and confounding. The ratings are carried as subscripts throughout the text so the reader can replace them with his own opinions if desired. The ratings are not intended as numerical weighting factors.

[2] KATA has no tier number because the odds ratio cannot be calculated.

250103905

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-2. Studies by location, time, size, and ETS exposure

Country	Study	Accrual[1] Period	Size[2] Cases	Size[2] Controls	ETS Exposure (%)[3] Cases	ETS Exposure (%)[3] Controls
Greece	KALA	1987-89	90	116	71	60
Greece	TRIC	1978-80	40	149	73	52
Hong Kong	CHAN	1976-77	84	139	60	53
Hong Kong	KOO	1981-83	86	136	59	49
Hong Kong	LAMT	1983-86	199	335	58	45
Hong Kong	LAMW	1981-84	60[4]	144[4]	62[4]	44[4]
Japan	AKIB	1971-80	94	270	78	70
Japan	HIRA(Coh)	1965-81	— 91,540 —		—— 76 ——	
Japan	INOU	1973-83	22	47	82	64
Japan	SHIM	1982-85	90	163	58	56
Japan	SOBU	1986-88	144	731	56	54
USA	BROW	1979-82	19	47	21	15
USA	BUFF	1976-80	41	196	80	84
USA	BUTL(Coh)	1976-82	— 9,207[5] —		—— 34[5] ——	
USA	CORR	1979-82	22	133	64	46
USA	FONT	1985-88	420	780[6]	70	63[6]
USA	GARF	1971-81	134	402	67	61
USA	GARF(Coh)	1959-72	— 176,739 —		—— 72 ——	
USA	HUMB	1980-84	20	162	75	56
USA	JANE	1982-84	191	191	77[7]	80[7]
USA	KABA	1961-80	24	25	54	60
USA	WU	1981-82	29[8]	62[8]	*	*

250103190

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-2. (continued)

Country	Study	Accrual[1] Period	Size[2] Cases	Size[2] Controls	ETS Exposure (%)[3] Cases	ETS Exposure (%)[3] Controls
W. Europe	HOLE(Coh)	1972-85	— 1,784 —		—— 73 ——	
Scotland						
England	LEE	1979-82	32	66	69	68
Sweden	PERS	1961-80	67	*	49	*
Sweden	SVEN	1983-85	34	174	71	66
China	GAO	1984-86	246	375	77	74
China	GENG	1983	54	93	63	44
China	LIU	1985-86	54	202	83	87
China	WUWI	1985-87	417	602	49	55

[1] Time during which cases occurred.
[2] Number of subjects included in ETS analyses; where numbers differ for spousal smoking and other exposures, those for spousal smoking are given.
[3] Spousal smoking unless otherwise noted.
[4] Adenocarcinoma only. Data for all cell types was only available for general passive smoke exposure, which showed 77% of 75 cases and 56% of 144 controls exposed.
[5] Figure pertains to "spouse pairs" cohort, which is of principal interest regarding ETS; a subgroup of this cohort comprised the "ASHMOG" cohort.
[6] Figure is for population controls; study also included 351 colon cancer controls (66% exposed).
[7] General ETS exposure; ORs but no exposure prevalences presented for spousal smoking.
[8] Adenocarcinoma only. Analyses for other cell types included smokers while adjusting for smoking status.

* Data not available.

25010319 07

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-3. Case-control studies of ETS: characteristics

Study	Percent proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
AKIB	90	88	70.2 35-95	* *	Atomic bomb survivor population	Age, sex, residence, med. exam participation[7]	Yes
BROW	69	39	66.3	68.2	Cancer cases[4]	Age, sex	No[3]
BUFF	82	76	30-79	30-79	Cancer cases[6]	Age, sex	No[3]
CHAN	*	*	39-70	39-70	Orthopedic patients	Matched but variables unspecified	No[3]
CORR	*	*	*	*	Hospital patients[8]	Age (± 5), sex, race	No[3]
FONT	34	0-10[23]	20-79	20-79	Cancer cases; general population	Age, (for cancer controls) race	Yes
GAO	0	*	35-69	35-69	General population	Age (± 5)	No[3]
GARF	88	*	≥40	≥40	Cancer cases[9]	Age (± 5), hospital	Yes
GENG	*	*	≤65	≤65	*	Age (± 2), sex, race, marital status	No[3]
HUMB	*	*	≤85	≤85	General population	Age (± 10), sex, ethnicity	No[3]
INOU	100	100	*	*	Cerebrovas-cular disease deaths	Age, year of death (± 2.5), district	No[3]
JANE	33[19]	33[19]	67.1[19]	68.1[19]	New York State Dept. of Motor Vehicles	Age, sex, county, smoking history	Yes

25010319 08

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-3. (continued)

Study	Percent proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
KABA	*	*	61.6	53.9	Patients[10]	Age (± 5), sex, race, hospital	Yes
KALA	0	0	≥35	≥35	Orthopedic Patients	Sex	Yes
KATA	0	0	67.8	*	Non-cancer patients	Age (± 2), sex	Yes
KOO	*	*	*	*	"Healthy"[11]	Age (± 5), residence, housing	No[3]
LAMT	*	*	*	*	"Healthy"[12]	Age (± 5), residence	No[3]
LAMW	*	*	67.5	66	Hospitalized orthopedic patients	Age, socio-economic status, residence[22]	No[3]
LEE	38[13]	38	35-74	35-74	Patients[14]	Age, sex, hospital location, time of interview	No[3,5]
LIU	0	0	52	52	General population?	Age (± 2), sex, village	Yes
PERS	*[15]	*	*[16]	*	*[17]	Age (± 1), sex	Yes
SHIM	*	*	59 35-81	58 35-81	Patients[18]	Age (± 1), hospital, admission date	Yes
SOBU	0	0	60	56	Patients	None	No
SVEN	0	0	66.3		General population	Age	No[3]
TRIC	*	*	62.8	62.3	Hospitalized orthopedic patients	Age, occupation, education[22]	No[3]

25010319 09

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-3. (continued)

Study	Percent proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
WU	*	*	<76	<76	Neighborhood[12]	Age (± 5), sex, race	No[3]
WUWI	0	0	55.9[20]	55.4[20]	General population	Sex, age[21]	No[3]

1 "Ca" and "Co" stand for "cases" and "controls," respectively.
2 Single values are the average or median. Paired values are the range.
3 Not matched on personal smoking status (e.g., smoker/nonsmoker).
4 Persons with cancers of bone marrow or colon in Colorado Control Cancer Registry.
5 Ongoing study modified for passive smoking.
6 Population-based and decedent comparison subjects selected from state and Federal records.
7 Participation in RERF biennial medical examination program.
8 Assorted ailments.
9 Colorectal cancer.
10 Diseases not related to smoking.
11 Selected from a healthy population.
12 Living in neighborhood of matched case.
13 Applies only to the 143 patients in the followup study.
14 Excluding lung cancer, chronic bronchitis, ischemic heart disease, and stroke.
15 No overall percentages given.
16 Two control groups: 15 to 65 and 35 to 85 for both cases and controls in groups 1 and 2, respectively.
17 Two control groups were randomly chosen from the cohort under study.
18 Patients in the same or adjacent wards with other diseases.
19 Includes males and females and long-term ex-smokers.
20 Entire study population, including smokers.
21 Frequency matched by 5-year age group to age distribution of cases reported in study area 2 years prior to initiation of study.
22 "Similar" but not actually matched.
23 0% for general population and 10% for colon cancer controls.

* Data not available.

25010310910

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-4. Estimated relative risk of lung cancer from spousal ETS by epidemiologic study (crude and adjusted for cofactors)

Case-control	Never-Smokers	
	Crude RR[1, 14]	Adj. RR[1, 2, 14]
AKIB	1.52 (0.96, 2.41)	1.5 (1.0, 2.5)
BROW	1.52[18] (0.49, 4.79)	*
	1.82[18] (0.45, 7.36)[5]	1.68[18] (0.39, 6.90)[5]
BUFF	0.81[12] (0.39, 1.66)	*
CHAN	0.75 (0.48, 1.19)	*
CORR	2.07[19] (0.94, 4.52)	*
FONT[26]	1.37 (1.10, 1.69)	1.29 (1.03, 1.62)
	1.21 (0.94, 1.56)	1.28 (0.98, 1.66)
	1.32 (1.08, 1.61)	*
GAO	1.19 (0.87, 1.63)	1.34[3,4]
GARF	1.31 (0.93, 1.85)	1.70[21] (0.98, 2.94)[5]
GENG	2.16 (1.21, 3.84)	*
HIRA[6]	1.53[3] (1.10, 2.13)	1.64[3] *
HUMB	2.34 (0.96, 5.69)	2.2 (0.9, 5.5)
INOU	2.55[13] (0.90, 7.20)	2.54[3, 7] *
JANE	0.86 (0.57, 1.29)	0.93/0.44[8]

25010319 11

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-4. (continued)

Case-control	Never-Smokers	
	Crude RR[1, 14]	Adj. RR[1, 2, 14]
KABA[22]	0.79 (0.30, 2.04)	*
KALA	1.62[9] (0.99, 2.65) 1.41 (0.78, 2.55)	1.92 (1.02, 3.59)[5] *
KATA	*[16]	*
KOO	1.55 (0.98, 2.44)	1.64
LAMT	1.65 (1.22, 2.22)	*
LAMW	2.51[17] (1.49, 4.23)	*
LEE	1.03 (0.48, 2.20)	0.75/1.60[10]
LIU	0.74 (0.37, 1.48)	0.77 (0.35, 1.68)
PERS	1.28 (0.82, 1.98)	1.2 (0.7, 2.1)[5]
SHIM	1.08[23] (0.70, 1.68)	*
SOBU	1.06[9] (0.79, 1.44) 1.77 (1.29, 2.43)	1.13[9] (0.78, 1.63)[5] 1.57 (1.07, 2.31)[5]
SVEN	1.26[11] (0.65, 2.48)	1.4[11]
TRIC	2.08[20] (1.31, 3.29)	*
WU	1.41[15] (0.63, 3.15)	1.2 (0.6, 2.5)[5]
WUWI	0.79 (0.64, 0.98)	0.7
BUTL (Coh)	2.45[24]	2.02 (0.48, 8.56)[5]

25010319 12

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-4. (continued)

Case-control	Never-Smokers		
	Crude RR[1, 14]		Adj. RR[1, 2, 14]
GARF (Coh)	*		**1.17**[3] (0.85, 1.61)[5]
HIRA (Coh)	**1.38** (1.03, 1.87)		1.61 *
HOLE[25] (Coh)	2.27 (0.40, 12.7)		1.99 (0.24, 16.7)[5]

[1] Parentheses contain 90% confidence limits, unless noted otherwise. When not represented in the original studies, the crude ORs and their confidence limits were calculated (or verified) by the reviewers wherever possible. Boldface indicates values used for analysis in text of this report. Odds ratios are shown for case-control studies; relative risk for cohort studies.

[2] Calculated by a statistical method that adjusts for other factors (see Table 5-3), but not corrected for smoker misclassification.

[3] Composite measure formed from categorical data at different exposure levels.

[4] For Gao, data are given as (number of years lived with a smoker, adj. OR): (< 20,1.0), (20-29, 1.1), (30-39, 1.3), (40+, 1.7).

[5] 95% confidence interval.

[6] Case-control study nested in the cohort study of Hirayama. OR for ever-smokers is taken from cohort study (shown in table below). This case-control study is not counted in any summary results where HIRA(Coh) is included.

[7] For Inoue, data are given as (number of cig./day smoked by husband, adj. OR): (<19,1.58), (20+, 3.09).

[8] From subject responses/from proxy responses.

[9] For the first value, "ETS-exposed" means the spouse smokes; for the second value, "ETS-exposed" means a member of the household other than the spouse smokes.

[10] From subject responses/from spouse responses.

[11] Exposure at home and/or at work.

[12] Exposure to regularly smoking household member(s). Differs slightly from published value of 0.78, wherein 0.5 was added to all exposure cells.

[13] OR reported in study is 2.25, in contrast to the value shown that was reconstructed from the confidence intervals reported in the study; no reply to inquiry addressed to author had been received by press time.

[14] ORs for never-smokers applies to exposure from spousal smoking, unless indicated otherwise.

[15] Raw data for Wu are from Table 11 of Surgeon General (1986). Data apply to adenocarcinoma only.

[16] Odds ratio is not defined because number of unexposed subjects is zero for cases or controls.

[17] Table entry is for exposure to smoking spouse, cohabitants, and/or coworkers; includes lung cancers of all cell types. The OR for spousal smoking alone is for adenocarcinoma only: 2.01 (90% C.I. = 1.20, 3.37).

[18] Adenocarcinoma only. Data and OR value communicated from author (Brownson).

[19] Excludes bronchioalveolar carcinoma. Crude OR with bronchioalveolar carcinoma included is reported to be 1.77, but raw data for calculation of confidence interval are not provided.

25010319 13

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-4. (continued)

[20] Known adenocarcinomas and alveolar carcinomas were excluded, but histological diagnosis was not available for many cases. Data are from Trichopoulos et al. (1983).

[21] Estimate for husband smoking 20 cig./day.

[22] For second KABA study (see addendum in study description of KABA), preliminary unpublished data and analysis based on ETS exposure in adulthood indicate 68% of never-smokers are exposed and OR = 0.90 (90% C.I. = 0.51, 1.58), not dissimilar from the table entry shown.

[23] From crude data, estimated to be: exposed cases 52, exposed controls 91, unexposed cases 38, unexposed controls 72.

[24] RR is based on person-years of exposure to spousal smoking. "Prevalence" in those units is 20%.

[25] RR values under never-smoker are for lung cancer mortality. For lung cancer incidence, crude RR is 1.51 (90% C.I. = 0.41, 5.48) and adj. RR is 1.39 (95% C.I. = 0.29, 6.61).

[26] The first, second, and third entries are calculated for population controls, colon cancer controls, and both control groups combined, respectively. For adenocarcinoma alone, the corresponding ORs, both crude and adjusted, are higher by 0.15-0.18.

Note: Values used for inference in this report are shown in boldface.

* Data not available.

250103191H

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-5. Effect of statistical adjustments for cofactors on risk estimates for passive smoking[16]

Case-Control Study	Exposure		Crude RR[6]	Adj RR[6]	Adjustment Factor(s)[1]	Adj Technique[4]
	Source[2]	Place[3]				
AKIB	Sp	A	1.52	1.5	A,L,O	LR
BROW	Sp	A	1.52	*	*	*
	A	P	1.82	1.68	A,I,O	LR
BUFF	Co	H	0.81	*	*	*
CHAN	A	A	0.75	*	*	*
CORR	Sp	A	2.07[13]	*	*	*
	M(C)	A	1.66[13]	1.36[13]	Sm	R
FONT	Sp	A	1.37[17]	1.29[17]	A,E,I,L,R	LR
	Sp	A	1.21[18]	1.28[18]	A,E,I,L,R	LR
GAO	Sp	A	1.19	1.34[9]	A,E	R
	A	A	*	0.9	A	LR
GARF	Sp	H	1.31	1.70	A,SES,H,Yd	R
GENG	Sp	A	2.16	*	*	*
HIRA	Sp	A	1.53[9]	1.64[9]	A,F,Oh,	S
	Sp	A	1.53	1.50	F	S
HUMB	Sp	A	2.34	2.2	A,R	R
INOU	Sp	A	2.55	2.54[9]	A,N	S
JANE	Sp	A	0.86	0.93/0.44[15]	A,L,R	M,S
	A(C)	H	*	1.09/2.07[5]	A,R	
KABA	Sp	A	0.79	*	*	*
KALA	Sp	A	1.62	1.92	A,E,Ir	LR
	OC	H	1.41	*	*	*
KOO	Sp	A	1.55	1.64	A,E,B,Yc	LR
	Co	H	1.34	1.68	A,E,B,Yc	LR

25010319

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-5. (continued)

Case-Control Study	Exposure Source[2]	Exposure Place[3]	Crude RR[6]	Adj RR[6]	Adjustment Factor(s)[1]	Adj Technique[4]
LAMT	Sp	A	**1.65**	*	*	*
LAMW	Sp	*	2.01[7]	*	*	*
	A	*	**2.51**[14]	*	*	*
LEE	Sp	A	1.3[8] 0.75 [1.03	1.60[8] 0.75 1.00]	A	S
	Co	H	0.80	0.87[9]	A	S
LIU	Co	A	0.74	**0.77**	C	LR
PERS	Sp	A	1.28	**1.2**	A,V	M
	Sp	A	1.28	1.47[9]	A	S
SHIM	Sp	H	**1.08**	*	*	*
SOBU	Sp	A	1.06	1.13	A,E	S
	OC	A	1.77	**1.57**	A,E	S
SVEN	A	H,W	1.1/1.8[10] (1.26)	1.2/2.1[10] (1.4)	A	S
TRIC	Sp	A	**2.08**	*	*	*
WU	Sp	A	**1.41**[11]	1.2	A,L As	M LR
WUWI	Sp	P	**0.79**	0.7	A,E,L	LR
	Co	P	0.78	0.7	A,E,L	LR
BUTL (Coh)	Sp	A	2.45	**2.02**	A	S
GARF (Coh)	Sp	A	*	1.27/1.10[12] **1.17** 1.37/1.04[12]	A A,E,L,R,Oh	S S
HIRA (Coh)	Sp	A	**1.38**	1.61	Ah	S
HOLE (Coh)	Co	A	2.27	**1.99**	A,SES	S

[1] Adjustment factors: A = age of subject; Ah = age of husband; As = age started smoking; B = number of live births; C = cooking habits; D = diet; E = education; F = fish consumption; G =

25010319 16

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-5. (continued)

gender; H = hospital; I = income; Ir = interviewer; L = location; M = marital status; O = occupation (of subject); Oh = occupation (of husband); R = racial or ethnic group; SES = socioeconomic status; Sm = active smoking; V = vital status; Yc = years since exposure ceased; Yd = year of diagnosis; Yi = year of interview.

[2] Source: A = Anyone; (C) = childhood; Co = cohabitant(s); M = mother; OC = cohabitant(s) other than spouse; Sp = spouse; W = coworker(s).

[3] Place: A = anywhere; H = home/household; P = proximity of subjects; W = workplace.

[4] LR = logistic regression; R = regression; M = matched analysis; S = stratified.

[5] 1-24 smoker-years/ $\geq$ 25 smoker-years.

[6] OR for case-control studies; RR for cohort studies.

[7] Adenocarcinoma only.

[8] First value is for smoking information provided by patient's spouse, second for information provided by patient herself, [third utilizes available data from either source(s) with subject classified as exposed if either source so indicates].

[9] Composite measure formed from categorical data at different exposure levels.

[10] Exposed at home but not at work or vice versa/Exposed both at home and at work followed by weighted average of exposed strata.

[11] Crude OR from Table 11 of Surgeon General (1986); note that Adj OR from WU is not restricted to never-smokers and analysis includes only adenocarcinoma.

[12] Spouse smokes 1-20 cig./day/spouse smokes $\geq$ 20 cig./day. The composite RR is 1.17.

[13] Bronchioalveolar carcinoma excluded. Spousal smoking OR = 1.77 with bronchioalveolar carcinoma excluded; no corresponding value reported for maternal smoking.

[14] All cell types.

[15] Cases and controls matched on A, L, and N; first value is from subject; second value is from proxy sources.

[16] Values used for inference in this report are shown in boldface.

[17] Population controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.52 and 1.47, respectively).

[18] Colon cancer controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.35 and 1.44, respectively).

* Data not available.

2501031917

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-6. Alternative estimates of lung cancer relative risks associated with active and passive smoking

Study	Active/ Passive	ETS Exposure	Alternative Controls Exp.(%)	Alternative Estimate	Comparison Estimate[8]
BUTL (Coh)	Act	N.A.[9]	14[10]	Adj. RR 4.0[11]	*
BUFF[1]	Pass	Household members regularly smoking for 33+ years	71	Crude OR 0.95 (0.38, 2.40)	0.81
FONT[15]	Pass	Spousal smoking, all types	63	Crude OR 1.52[12] (1.19, 1.96)	1.37
				Adj. OR 1.47	1.29
			66	Crude OR 1.35[13] (1.02, 1.80)	1.21
				Adj. OR 1.44	1.28
			64	Crude OR 1.47[14] (1.15, 1.87)	1.32
				No Adj. OR	*
HUMB[2]	Pass	Spousal cigarette smoking[2]	57	Crude OR 1.8 (0.6, 5.4)	2.3
				Adj. OR 1.7	2.2
KOO[3]	Pass	Home and/or workplace exposure over lifetime[3]	64	Crude OR 1.36 (0.83, 2.21)	1.34
				Adj. OR 1.86	1.64
PERS[4]	Act	N.A.[9]	37[10]	Crude OR 4.2	*
SHIM[5]	Pass	Total household ETS exposure[5]	77	Crude OR 1.36	1.08
HIRA[6] (Coh)	Act	N.A.[9]	44[10]	Adj. RR 3.79	2.67
HOLE[7] (Coh)	Act	N.A.[9]	56[10]	Adj. RR 4.2	*

[1] Values in Tables 5-4 and 5-5 include household smoking for any duration. Lung cancer may have a long latency period, however, so the extended exposure may be of interest.

[2] Values in Tables 5-4 and 5-5 include spousal smoking of cigars and pipes.

[3] Value in Table 5-5 is for household cohabitant smoke exposure during adulthood.

250103191B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-6. (continued)

[4] Estimate is based on papers by Cederlof et al. (1975) and Floderus et al. (1988) describing larger populations on which Pershagen study was based.
[5] Composite estimate from crude ORs for exposure from husband, parents, and father-in-law. Values in Tables 5-4 and 5-5 consider only spousal smoke exposure.
[6] Compares active smokers with never-smokers unexposed to ETS, thus providing a reference group more truly unexposed to tobacco smoke. The value in Table 5-4 is the more conventional comparison of ever-smokers with never-smokers, regardless of passive smoking status.
[7] Estimate is from adjusted RR for both sexes combined with assumption that female RR is 75% of male RR.
[8] Nearest equivalent from Tables 5-4 or 5-5.
[9] Not applicable because alternative estimate is for active smoking.
[10] Percent ever-smokers.
[11] Rough estimate based on data in Fraser et al. (1991). The prevalence of female ever-smoking is estimated from KALA and TRIC, similar conservative societies.
[12] Population controls only.
[13] Colon cancer controls only.
[14] Control groups combined.
[15] As in Table 5-4 except for adenocarcinoma alone.

* Data not available.

25010319 19

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-7. Estimated correction for smoker misclassification

Case Control	Never-Smokers RR[7] Uncorrected[1] (1)		Corrected[5] (2)	Bias[3] (1)/(2)	Ever-Smokers OR Used[2]
AKIB	_____	1.5 (1.0, 2.5)	_____	1.00	2.38
BROW	1.52 (0.49, 4.79)		1.50 (0.48, 4.72)	1.01	4.30
BUFF	0.81 (0.39, 1.66)		0.70 (0.34, 1.43)	1.16	7.06
CHAN	0.75 (0.48, 1.19)		0.74 (0.47, 1.17)	1.01	3.48
CORR	2.07 (0.94, 4.52)		1.90 (0.86, 4.15)	1.09	12.40
FONT	1.29 (1.03, 1.62)		1.26 (1.01, 1.58)	1.03	8.0
GAO	_____	1.19 (0.87, 1.63)	_____	1.00	2.54
GARF	1.31 (0.93, 1.85)		1.24 (0.88, 1.76)	1.06	6.0
GENG	_____	2.16 (1.21, 3.84)	_____	1.00 (0.995)	2.77
HIRA	1.53 (1.10, 2.13)		1.52 (1.10, 2.12)	1.01	3.20
HUMB	2.2 (0.9, 5.5)		1.98 (0.8, 5.0)	1.11	16.3
INOU	_____	2.55 (0.90, 7.20)	_____	1.00 (0.996)	1.66
JANE	0.86 (0.57, 1.29)		0.78 (0.51, 1.16)	1.10	8.0
KABA	0.79 (0.30, 2.04)		0.74 (0.28, 1.90)	1.07	5.90
KALA	_____	1.92 (1.13, 3.23)[4]	_____	1.00	3.32
KATA	*		*	*	*
KOO	1.55 (0.98, 2.44)		1.54 (0.98, 2.43)	1.01	2.77

05/15/92
250103920
Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-7. (continued)

Case Control	Never-Smokers RR[7] Uncorrected[1] (1)		Corrected[5] (2)	Bias[3] (1)/(2)	Ever-Smokers OR Used[2]
LAMT	1.65 (1.21, 2.21)		1.64 (1.21, 2.21)	1.01	3.77
LAMW	———	2.51 (1.49, 4.23)	———	1.00 (0.996)	4.12
LEE	1.03 (0.48, 2.20)		1.01 (0.47, 2.15)	1.02	4.61
LIU	———	0.77 (0.35, 1.68)	———	1.00	*
PERS	1.2 (0.7, 2.1)[4]		1.17 (0.75, 1.87)[4]	1.03	4.2
SHIM	1.08 (0.70, 1.68)		1.07 (0.7, 1.67)	1.01	2.8
SOBU	———	1.57 (1.13, 2.15)[4]	———	1.00	2.81
SVEN	1.26 (0.65, 2.48)		1.19 (0.62, 2.35)	1.06	6.00
TRIC	———	2.08 (1.31, 3.29)	———	1.00	2.81
WU	1.41 (0.63, 3.15)		1.31 (0.58, 2.92)	1.08	4.38
WUWI	0.79 (0.64, 0.98)		0.78 (0.63, 0.96)	1.01	2.24
BUTL (Coh)	2.02 (0.48, 8.56)[4]		2.01 (0.61, 6.73)[4]	1.00	4.0
GARF (Coh)	1.17 (0.85, 1.61)[4]		1.15 (0.88, 1.51)	1.02	3.5
HIRA (Coh)	1.38 (1.03, 1.87)		1.37 (1.02, 1.86)	1.01	3.20
HOLE (Coh)	1.99 (0.24, 16.7)[4]		1.97 (0.34, 11.67)[4]	1.01	4.2[6]

[1] Adjusted OR in Table 5-4 is used unless the confidence interval is unknown or the study review (Appendix A) is critical of the method(s) used.

[2] The crude OR for ever-smokers in Table 5-4 is used in the calculations for the corrected value (Appendix B), when available. Ever-smoker ORs for GARF, JANE, PERS, and SHIM are

250103192

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-7. (continued)

approximated from the data of other studies for suitable location and time period. The ever-smoker OR for BUTL(Coh) [LEE] is based on data in Fraser (1991) [Alderson et al. (1985)].

[3] Values shown are min(calculated ratio, 1). Calculated ratios less than 1 are shown in parentheses.

[4] 95% confidence interval.

[5] Corrected (2) (estimate and confidence interval) equals uncorrected (1) times ratio [(2)/(1)]. All corrected 95% confidence intervals have been converted to 90% confidence intervals.

[6] Adjusted RR value in Table 5-6.

[7] OR for case-control studies; RR for cohort studies.

25010319 22

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-8. Statistical measures by individual study and pooled by country, corrected for smoker misclassification[1]

Location	Study	Relative Weight[2] (%)	Power[3]	p-value Effect[4]	p-value Trend[5]	RR[6]	Confidence Interval 90%
Greece	KALA	43	0.39	0.02	0.04	1.92	(1.13, 3.23)
Greece	TRIC	57	0.45	0.01	<0.01	2.08	(1.31, 3.29)
Greece	**ALL**	**5**		**<0.01**		**2.00**	**(1.42, 2.83)**
HK	CHAN	20	0.43	>0.5	*	0.74	(0.47, 1.17)
HK	KOO	20	0.43	0.06	0.16	1.54	(0.98, 2.43)
HK	LAMT	45	0.73	<0.01	<0.01	1.64	(1.21, 2.21)
HK	LAMW	15	0.39	<0.01	*	2.51	(1.49, 4.23)
HK	**ALL**	**15**		**<0.01**		**1.48**	**(1.21, 1.81)**
Japan	AKIB	15	0.42	0.05	0.03	1.50	(1.00, 2.50)
Japan	HIRA (Coh)	35	0.75	0.04	<0.01	1.37	(1.02, 1.86)
Japan	INOU	3	0.17	0.07	<0.03	2.55	(0.90, 7.20)
Japan	SHIM	16	0.37[7]	0.39	*	1.07	(0.70, 1.67)
Japan	SOBU	30	0.66	0.01	*	1.57	(1.13, 2.15)
Japan	**ALL**	**19**		**0.01**		**1.43**	**(1.20, 1.71)**
USA	BROW	1	0.15	0.28	*	1.50	(0.48, 4.72)
USA	BUFF	3	0.17	>0.5	*	0.70	(0.34, 1.43)
USA	BUTL (Coh)	1	0.18	0.17	*	2.01	(0.61, 6.73)
USA	CORR	3	0.22	0.09	0.01	1.90	(0.86, 4.15)
USA	FONT[8]	35	0.93	0.04	0.04	1.26	(1.01, 1.58)

250103192 3

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-8. (continued)

Location	Study	Relative Weight[2] (%)	Power[3]	p-value Effect[4]	p-value Trend[5]	RR[6]	Confidence Interval 90%
USA	GARF	15	0.60[7]	0.15	<0.02	1.24	(0.88, 1.76)
USA	GARF (Coh)	25	0.92	0.19	*	1.15	(0.88, 1.51)
USA	HUMB	2	0.20	0.10	ns	1.98	(0.81, 4.95)
USA	JANE	10	0.44[7]	>0.5	*	0.78	(0.51, 1.16)
USA	KABA	2	0.17[7]	>0.5	*	0.74	(0.28, 1.90)
USA	WU	3	0.21	0.29	ns	1.31	(0.58, 2.92)
USA	**ALL**	**34**		**0.02**		**1.19**	**(1.04, 1.35)**
Scotland	HOLE (Coh)	100	0.09	0.26	*	1.97	(0.34, 11.67)
Eng./Wales	LEE	100	0.20	0.50	*	1.01	(0.47, 2.15)
Sweden	PERS	68	0.45[7]	0.22	0.12	1.17	(0.75, 1.87)
Sweden	SVEN	32	0.24	0.32	*	1.19	(0.62, 2.35)
W. Europe	**ALL**	**5**		**0.21**		**1.17**	**(0.84, 1.64)**
China	GAO	28	0.66	0.19	0.29	1.19	(0.87, 1.62)
China	GENG	8	0.32	0.01	<0.05	2.16	(1.21, 3.84)
China	LIU	4	0.18	>0.5	*	0.77	(0.35, 1.68)
China	WUWI	60	0.89[7]	>0.5	*	0.78	(0.63, 0.96)
China	**ALL**	**22**		**>0.5**		**0.95**	**(0.80, 1.12)**
China	**GAO and GENG**			**0.03**		**1.36**	**(1.03, 1.79)**

[1] * means information is not available.

[2] A study's relative weight (wt) is 1/var (log(OR)), divided by the sum of those terms for all studies included, times 100 (to express as a percentage). Study weights shown for whole countries are with WUWI included for China.

25010319 24

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-8. (continued)

[3] *A priori* probability of significant ($p < 0.05$) test of effect when true relative risk is 1.5.
[4] One-sided p-value for test of $RR = 1$ versus $RR > 1$.
[5] p-value for upward trend. p-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative, i.e., upward trend.
[6] Adjusted for smoker misclassification. OR used for case-control studies; RR for cohort studies.
[7] Calculated for matched study design.
[8] For population control group only, all cases.

2501031925

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-9. Case-control and cohort studies: exposure response trends for females

Study	Case	Cont.	Exposure[4]	RR[14]	C.I.[1]	p-Trend[15]
AKIB	21	82		1.0		0.03
(cig./day)	29	90	1-19	1.3	(0.7, 2.3)[2]	
	22	54	20-29	1.5	(0.8, 2.8)[2]	
	12	23	≥30	2.1	(0.7, 2.5)[2]	
AKIB	21	82	0	1.0		0.24
(years)	20	30	1-9	2.1	(1.0, 4.3)[2]	
	29	81	20-39	1.5	(0.8, 2.7)[2]	
	22	59	≥40	1.3	(0.7, 2.5)[2]	
CORR	8	72	0	1.00		0.01
(pack-yrs.)	5	38	1-40	1.18	(0.44, 3.20)	
	9	23	≥41	3.52	(1.45, 8.59)	
FONT[5]	*	*	0	1.00		0.07
(years)	*	*	1-15	1.19	(0.88, 1.61)	
	*	*	16-30	1.14	(0.82, 1.59)	
	*	*	>30	1.25	(0.91, 1.72)	
FONT[16]	*	*	0	1.00		0.02
(years)	*	*	1-15	1.33	(0.93, 1.89)	
	*	*	16-30	1.40	(0.96, 2.05)	
	*	*	>30	1.43	(0.99, 2.09)	
FONT[5]	*	*		1.00		0.04
(pack-yrs.)	*	*	0<15	0.96	(0.72, 1.29)	
	*	*	15-39	1.13	(0.81, 1.59)	
	*	*	40-79	1.25	(0.86, 1.81)	
	*	*	≥80	1.33	(0.68, 2.58)	
FONT[16,5]	*	*		1.00		0.01
(pack-yrs.)	*	*	0<15	1.03	(0.73, 1.46)	
	*	*	15-39	1.26	(0.85, 1.87)	
	*	*	40-79	1.49	(0.98, 2.27)	
	*	*	≥80	1.70	(0.82, 3.49)	
GAO	99	57	0-19	1.0		0.29
(tot. yrs.)[3]	93	63	20-29	1.1	(0.7, 1.8)	
	107	78	30-39	1.3	(0.8, 2.1)	
	76	48	≥40	1.7	(1.0, 2.9)	
GARF	44	157	0	1.00		<0.02
(cig./day)	29	90	1-9	1.15	(0.8, 1.6)	
	17	56	10-19	1.08	(0.8, 1.5)	
	26	44	≥20	2.11	(1.1, 4.0)	

25010319 26

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-9. (continued)

Study	Case	Cont.	Exposure[4]	RR[14]	C.I.[1]	p-Trend[15]
GENG	*	*	0	1.00		<0.05[8]
(cig./day)	*	*	1-9	1.40	(1.1, 1.8)	
	*	*	10-19	1.97	(1.4, 2.7)	
	*	*	≥20	2.76	(1.9, 4.1)	
GENG	*	*	0	1.00		<0.05[8]
(years)	*	*	<20	1.49	(1.15, 1.94)	
	*	*	20-39	2.23	(1.54, 3.22)	
	*	*	≥40	3.32	(2.11, 5.22)	
HUMB	*	*	0	1.0		ns
(cig./day)	*	*	1-20	1.8	(0.6, 5.6)[2]	
	*	*	≥21	1.2	(0.3, 5.2)[2]	
INOU	*	*	0-4	1.00		<0.03
(cig./day)	*	*	5-19	1.58	(0.4, 5.7)[2]	
	*	*	≥20	3.09	(1.0, 11.8)[2]	
KALA	26	46	0	1.00		0.08
(cig./day)	34	39	1-20	1.54	(0.88, 2.70)	
	22	22	21-40	1.77	(0.93, 3.35)	
	8	9	41+	1.57	(0.64, 3.85)	
KALA	26	46	0	1.00		0.04
(years)	15	21	<20	1.26	(0.56, 2.87)	
	15	20	20-29	1.33	(0.58, 3.03)	
	17	15	30-39	2.01	(0.86, 4.67)	
	17	16	≥40	1.88	(0.82, 4.33)	
KOO	32	67	0	1.00		0.16
(cig./day)	17	15	1-10	2.33	(0.9, 5.9)	
	25	35	11-20	1.74	(0.8, 3.8)	
	12	19	≥21	1.19	(0.5, 3.0)	
LAMT[5]	84	183	0	1.00		0.01
(cig./day)	22	22	1-10	2.18	(1.14, 4.15)	
	56	66	11-20	1.85	(1.19, 2.87)	
	20	21	≥21	2.07	(1.07, 4.03)	
LAMT[16]	53	92	0	1.00		0.01
(cig/day)	17	12	1-10	2.46	(1.09, 5.54)	
	37	28	11-20	2.29	(1.26, 4.16)	
	15	9	≥21	2.89	(1.18, 7.07)	

250103927

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-9. (continued)

Study	Case	Cont.	Exposure[4]	RR[14]	C.I.[1]	p-Trend[15]
PERS[7]	34	*	0	1.0		0.12
(cig./day)	26	*	1-15	1.0	(0.6, 1.8)	
	7	*	≥16	3.2	(1.0, 9.5)	
TRIC[9]	24	109	0	1.00		0.01
(cig./day)	24	56	1-20	1.95	(1.13, 3.36)	
	14	25	≥21	2.55	(1.31, 4.93)	
WU[11]	*	*	0	1.0		ns
(years	*	*	1-30	1.2	*	
exposed as adult)	*	*	≥31	2.0	*	
GARF[12] (Coh)	65	*	0	1.00		*
(cig./day)	39	*	1-19	1.27	(0.85, 1.89)	
	49	*	≥20	1.10	(0.77, 1.61)	
HIRA[13] (Coh)	37	21,895	0	1.00		0.01
(cig./day)	99	44,184	1-19[10]	1.41	(1.03, 1.94)	
	64	25,461	≥20	1.93	(1.35, 2.74)	
	*		0	1.0		*
	*		1-15	0.8	*	
	*		>15	1.8	*	

[1] Confidence intervals are 95% unless noted otherwise.
[2] 90% confidence interval.
[3] Years lived with a smoking husband.
[4] Smoking by spouse unless otherwise specified.
[5] All histologies.
[6] Very limited number of cases (6 total) and no C.I. information available.
[7] Low exposure level is for husband smoking up to 15 cigarettes per day or one pack (50 g) of pipe tobacco per week, or smoking any amount during less than 30 years of marriage. High exposure level is for husband smoking more than 15 cigarettes per day or one pack of pipe tobacco per week during 30 years of marriage or more.
[8] Neither crude data nor a test for trend is included in reference articles. The relative risk at each exposure category is significant alone, however, at $p < 0.05$.
[9] Data from Trichopoulos et al. (1983), with RRs corrected (see letter, Trichopoulos, 1984).
[10] Includes former smokers of any exposure level.
[11] Years of exposure to spousal smoke *plus* years of exposure to workplace smoke; adenocarcinomas only.
[12] Value under RR is mortality ratio of observed to expected lung cancer deaths. Value under "Case" is number of observed lung cancer deaths.
[13] Standardized for age of subject (Hirayama, 1984). Values under "Case" are numbers of lung cancer deaths; values under "Cont." are total population.
[14] OR for case-control studies; RR for cohort studies.

250103928

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-9. (continued)

[15] p-value for upward trend. p-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative (i.e., upward trend). Values below 0.01 are shown as 0.01.

[16] Adenocarcinomas only.

* Data not available.

25010319 29

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-10. Reported p-values of trend tests for ETS exposure by study[1]

	Trend Test Results		
	Intensity (cig/day)	Duration (total years)	Cumulative (pack-years)[6]
AKIB	0.03	0.24	*
CORR	*	*	0.01
FONT	*	0.07[2]	0.04
	*	<0.02[3]	<0.01
GAO	*	0.29	*
GARF	<0.02	*	*
GENG	<0.05[4]	<0.05[4]	*
HUMB	ns	*	*
INOU	<0.03	*	*
KALA	0.08	0.04	*
KOO	0.16	*	*
LAMT	<0.01	*	*
	<0.01[3]		
PERS	0.12	*	*
TRIC	<0.01	*	*
WU	*	ns	*
GARF(Coh)	*[5]	*	*
HIRA(Coh)	<0.01	*	*
HOLE(Coh)	*[5]	*	*

[1] Detailed data presented in Table 5-9.
[2] All cell types.
[3] Adenocarcinoma only.
[4] Same footnote as for GENG, Table 5-9.
[5] Trend results presented without p-values or raw data--see Table 5-9.
[6] A "pack-year" is equivalent to one pack/day for 1 year.

* Data not available.

25010319 30

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-11. P-values of tests for effect and for trend by individual study[1]

Country	Study	Power	Test	p-value[2]
Greece	KALA	0.39	Effect	0.02
			Trend	0.04
Greece	TRIC	0.45	Effect	0.01
			Trend	<0.01
Hong Kong	CHAN	0.43	Effect	>0.50
Hong Kong	KOO	0.43	Effect	0.06
			Trend	0.16
Hong Kong	LAMT	0.73	Effect	<0.01
			Trend	<0.01
Hong Kong	LAMW	0.39	Effect	0.01
Japan	AKIB	0.42	Effect	0.05
			Trend	<0.03
Japan	HIRA(Coh)	0.75	Effect	0.04
			Trend	<0.01
Japan	INOU	0.17	Effect	0.07
			Trend	0.03
Japan	SHIM	0.37	Effect	0.39
Japan	SOBU	0.66	Effect	0.01
USA	BROW	0.15	Effect	0.28
USA	BUFF	0.17	Effect	>0.50
USA	BUTL(Coh)	0.18	Effect	0.17
USA	CORR	0.22	Effect	0.09
			Trend	0.01
USA	FONT	0.93	Effect	0.04[3]
			Trend	0.04[3]
USA	GARF	0.60	Effect	0.15
			Trend	<0.02

25010319 31

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-11. (continued)

Country	Study	Power	Test	p-value[2]
USA	GARF(Coh)	0.92	Effect	0.19
USA	**HUMB**	0.20	**Effect** Trend	**0.10** n.s.
USA	JANE	0.44	Effect	>0.50
USA	KABA	0.17	Effect	>0.50
USA	WU	0.21	Effect	0.29
W. Europe				
Scot	Hole(Coh)	0.09	Effect	0.26
Eng	LEE	0.20	Effect	0.50
Sweden	**PERS**	0.45	Effect Trend	0.22 0.12
Sweden	SVEN	0.24	Effect	0.32
China	GAO	0.66	Effect Trend	0.19 0.29
China	**GENG**	0.32	**Effect** **Trend**	**0.01** **<0.05**
China	LIU	0.18	Effect	>0.50
China	WUWI	0.89	Effect	>0.50

[1] Test for effect -- H_0: no increase in lung cancer incidence in never-smokers exposed to spousal ETS; H_A: an increase. Test for trend -- H_0: no increase in lung cancer incidence as exposure to spousal ETS increases; H_A: an increase. p-values less than 0.1 are in boldface.

[2] Smallest p-value is used when there is more than one test for trend.

[3] For all cell types. p-values for adenocarcinoma alone were smaller.

250103193

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-12. Other risk-related factors for lung cancer evaluated in selected studies

Category	Possible Risk Factor	Mixed Outcome	No Evidence
Personal or family history	WU(USA) GENG(Ch) LIU(Ch)	SHIM(Jap) GAO(Ch)	
Heat source for cooking or heating	WU(USA) WUWI(Ch) GENG(Ch) GAO(Ch) LIU(Ch)	SOBU(Jap)	LAMW(HK)
Cooking with oil	WUWI(Ch) GAO(Ch)		
Diet	WU(USA)	KALA(Gr) HIRA(Jap)	SHIM(Jap)
Beta-Carotene			WUWI(Ch) KALA(Gr) GAO(Ch)-harmful
Occupation	WUWI(Ch) SHIM(Jap) GENG(Ch) BUTL(USA) BUFF(USA)		WU(USA) GAO(Ch)

250103193

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-13. Dietary effects in passive smoking studies of lung cancer in females

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
CORR[2]	2.07	Carotene Vitamin A	No data given No data given				Never-smokers. Carotene and total vitamin A were examined. "Except for gender, age, and study area, no confounding was detected."
GAO	1.19	Carotene rich Retinol rich Vitamin A index	1.0 1.0 1.0	1.0 1.1 1.6[3]	1.3 1.0 1.2	2.0[3] 1.1 2.0[3]	Patterns were similar for smokers and nonsmokers. Passive RR was not adjusted for diet, possibly because the trends were opposite those in the literature.
HIRA[4]	1.53	Green-yellow veg Fish Meat Milk Soy paste soup	- - - - -	1.0[5] 1.0 1.0 1.0 1.0	- - - - -	0.86[6] 1.87[3] 0.62 1.30 0.93	Never-smokers. Lung cancer risks for wives whose husbands were former smokers plus 1-19/day smokers and 20+/day smokers relative to never- smokers were 1.50 and 1.79 when adjusted for wives' age (Hirayama, 1984). They ranged from 1.53 to 1.69 and 1.66 to 1.91 when adjusted for wives' age, husband's occupation, and each of the various dietary factors.
KALA	1.92	β-carotene Vegetables Fruits Vitamin C Retinol (preformed)	1.0 1.0 1.0 1.0 1.0	- - - - -	- - - - -	1.01 1.09 0.33[3] 0.67 1.31	Never-smokers. Controlled for age, years of schooling, interviewer, and total energy intake. No confounding was observed between the passive smoking effect and the effect of fruits, or between that of fruits and that of vegetables. Passive risk increased to 2.11 when adjusted for fruit consumption.

DRAFT--DO NOT QUOTE OR CITE

250103193H
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-13. (continued)

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
KOO	1.55	Leafy green veg.	-	1.0	0.49	0.49	Never-smokers. Values are adjusted for age, numbers of live births, and schooling. Diet items are selected to compare with those in other studies. No calculation is shown of confounding effect of diet on the passive smoking risk either in Koo et al. (1987), Koo (1988), Koo et al. (1988), or Koo (1989). Fresh fruit, vitamin C, fresh fish, and retinol showed statistically significant trends.
		Carrots	-	1.0	1.31	0.51	
		β-carotene	-	1.0	0.73	0.73	
		Fresh fruit	-	1.0	0.81	0.42	
		Vitamin C	-	1.0	0.55	0.47	
		Fresh fish	-	1.0	0.46	0.35	
		Smoked/cured meat/poultry	-	1.0	0.82	0.92	
		Milk	-	1.0	1.66	0.92	
		Retinol	-	1.0	0.55	0.42	
SHIM	1.08	Green-yellow veg.	-	1.0[8]	-	0.9[8]	Never-smokers. No dose response was found. No difference between cases and controls was found regarding intake of green-yellow vegetables.
		Fruit	-	1.0	-	1.2	
		Milk	-	1.0	-	1.0	
		Fish, pork, or lamb	-	1.0	-	1.0	
		Chicken	-	1.0	-	0.7	
SVEN	1.26	Carrots	1.0[9]	0.7[10]	-	0.6[3,11]	Adjusted for age, smoking, cumulated Rn exposure and municipality. The inclusion of carrot consumption in the regression model "had only a slight effect on the risk estimates of the other exposure variables." See Svensson (1988).
WU	1.41	β-carotene	1.0	0.52	0.32	0.40[3]	For adenocarcinoma. Risks of 0.67, 1.0, and 0.63, high calf versus low calf, were observed for β-carotene, preformed vitamin A, and dairy and eggs for squamous cell carcinoma. Adjusted for cigarettes smoked per day. No adjustment is shown to the passive risk for diet.
		Preformed Vit. A	1.0	0.92	0.50	0.83	
		Dairy products and eggs	1.0	0.82	0.63[3]	0.37[3]	

DRAFT--DO NOT QUOTE OR CITE

05/15/92 2501031935

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-13. (continued)

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
WUWI	0.79	Vegetables	1.0	1.1	1.0	0.9	Adjusted for age, education, personal smoking, and study area. Eight variables other than smoking were thought to have a significant effect on lung cancer risk. Diet variables were not included in this list, and no adjustment to the passive risk was made for them.
		high-carotene	1.0	1.0	1.0	0.8	
		low-carotene	1.0	1.0	1.4[3]	1.5[3]	
		Fresh fruit	1.0	1.6[3]	1.6[3]	2.3[3]	
		Animal protein					

[1] From Table 2.
[2] As reanalyzed by Dalager et al. (1986).
[3] Statistically significant at the 95% level.
[4] Case control study nested in Hirayama's cohort study, ages 40-69 only; Hirayama, 1989.
[5] Less than daily.
[6] Daily.
[7] From Koo (1988a).
[8] Cut-offs various.
[9] Less than once per week.
[10] Once per week.
[11] More than once per week.

DRAFT--DO NOT QUOTE OR CITE

2501031936

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-14A. Study limitations and sources of uncertainty

Study	Classification				
	ETS Subjects	ETS Exposure	Cases	Controls	Representativeness
AKIB			X	X	X
BROW		X	X	X	
BUFF		X		X	X
CHAN		X	X	X	X
CORR	X			X	
FONT	X				
GAO		X	X	X	
GARF		X			
GENG	X		X	X	
HUMB				X	
INOU	X	X	X		X
JANE	X	X			
KABA		X		X	
KALA		X		X	
KATA		X			
KOO				X	
LAMT				X	
LAMW				X	
LEE		X	X		
LIU		X	X	X	
PERS					
SHIM	X	X			
SOBU				X	
SVEN				X	
TRIC	X		X	X	
WU			X	X	
WUWI	X		X	X	
BUTL (Coh)	X				X

25010319 37

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-14A. (continued)

Study	Classification				
	ETS Subjects	ETS Exposure	Cases	Controls	Represen-tativeness
GARF (Coh)		X	X		X
HIRA (Coh)	X	X	X		X
HOLE (Coh)			X		

2501031938

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-14B. Study limitations and sources of uncertainty2

	Collection			Analysis		
Study	Self-Questionnaire	Response and Follow-up	Proxy Response	Unmarrieds	Adjusted Analysis	Trend Analysis
AKIB		X	X			
BROW			X	X	X	X
BUFF		X	X	X	X	
CHAN		X			X	
CORR			X	X	X	
FONT					X	
GAO					X	
GARF			X	X		
GENG		X	X	X	X	
HUMB			X			X
INOU			X	X		
JANE				X	X	
KABA					X	
KALA						
KATA		X	X	X	X	
KOO				X	X	
LAMT				X	X	
LAMW					X	
LEE		X	X	X	X	
LIU				X	X	
PERS	X		X	X		
SHIM	X			X	X	
SOBU	X				X	
SVEN				X		
TRIC					X	
WU		X		X	X	X
WUWI				X	X	
BUTL (Coh)	X	X				
GARF (Coh)	X	X				
HIRA (Coh)					X	
HOLE (Coh)	X	X				

25010319

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-15. Diagnosis, confirmation, and exclusion of lung cancer cases

Study	Diagnosis/Confirmation[1] (%)				Excluded Secondary LC[5]
	Histology	Cytology	Radio./ Clinical	Other/ Unspec.	
AKIB[2]	53	4	43	0	Y
BROW	100				Y
BUFF[2,3]	100				Y
CHAN[2,3]	82			18	N
CORR[2]	97			3	Y
FONT	100				Y
GAO[2,6]	43	38	19	10	Y
GARF[6]	100				Y
GENG[2]	85		4	11	N
HUMB[8,9]	83			17	Y
INOU	*	*	*	*	N
JANE[2]	99		1		Y
KABA	100				Y
KALA	48	38		14	Y
KATA	100				N
KOO	94			6	Y
LAMT	100				Y
LAMW	100				Y
LEE	*	*	*	*	N
LIU[10]	17		83	0	N
PERS	83	16		1	Y
SHIM	100				Y
SOBU	100				Y

25010319 40

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-15. (continued)

Study	Diagnosis/Confirmation[1] (%) Histology	Cytology	Radio./ Clinical	Other/ Unspec.	Excluded Secondary LC[5]
SVEN[2]	70	29		1	Y
TRIC[2]	28	37	35		N
WU	100				Y
WUWI[2]	42	32	26		Y
BUTL (Coh)[4]	100				Y
GARF (Coh)	*	*	*		N
HIRA (Coh)	*	*	*		N
HOLE (Coh)[7]	*	*	*		N

[1] Figures apply to confirmation of original diagnosis when conducted.
[2] Not restricted to never-smokers (contains former smokers or ever-smokers).
[3] Inconsistency in article. May be 100% histology.
[4] Includes one former smoker.
[5] Y (for yes) if specifically indicated; otherwise, N.
[6] Diagnostic information was reviewed for study.
[7] Death certificate diagnosis checked against Scottish cancer registry records.
[8] Includes males.
[9] Available histologic specimens (17 cases) reviewed by pathologists. Poor agreement between review diagnoses and original cancer registry diagnoses (8 of 17 cases). Only reviewed cases, however, are presented in article.
[10] Includes male ever- and never-smokers and one female ever-smoker (control).

* Data not available.

250103194

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-16. Classification of studies by tier

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
Greece	KALA	X			
Greece	TRIC		X		
Hong Kong	KOO		X		
Hong Kong	LAMT		X		
Hong Kong	LAMW			X	
Hong Kong	CHAN				X
Japan	AKIB		X		
Japan	HIRA(Coh)		X		
Japan	SHIM			X	
Japan	SOBU			X	
Japan	INOU				X
USA	FONT	X			
USA	BUTL(Coh)		X		
USA	GARF		X		
USA	HUMB		X		
USA	JANE		X		
USA	WU		X		
USA	BROW			X	
USA	BUFF			X	
USA	CORR			X	
USA	GARF(Coh)			X	
USA	KABA			X	

25010319 42

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-16. (continued)

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
W. Europe					
Scot	HOLE(Coh)	X			
Sweden	PERS		X		
Sweden	SVEN		X		
England	LEE			X	
China	GAO			X	
China	GENG				X
China	LIU				X
China	WUWI				X

250103194

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 5-17. Summary data interpretation by country[4]

Through Tier[1]	Weight[2] (%)	Country[3]	Studies Added	RR	90% C.I.	p-value
1		Greece	KALA	1.92	(1.13, 3.23)	0.02
2	**9**	**Greece**	**TRIC**	**2.00**	**(1.42, 2.83)**	**0.0005**
2	**17**	**Hong Kong**	**KOO, LAMT**	**1.61**	**(1.25, 2.06)**	**0.0009**
3		Hong Kong	LAMW	1.75	(1.39, 2.19)	0.00002
4		Hong Kong	CHAN	1.48	(1.21, 1.81)	0.0008
2	**17**	**Japan**	**AKIB, HIRA(Coh)**	**1.44**	**(1.12, 1.85)**	**0.008**
3		Japan	SHIM, SOBU	1.41	(1.17, 1.68)	0.0009
4		Japan	INOU	1.43	(1.20, 1.71)	0.0005
1		USA	FONT	1.26	(1.01, 1.58)	0.04
2	**40**	**USA**	**BUTL(Coh), GARF, HUMB, JANE, WU**	**1.19**	**(1.02, 1.40)**	**0.04**
3		USA	BROW, BUFF, CORR, GARF(Coh), KABA	1.19	(1.04, 1.35)	0.02
1		W. Europe	HOLE(Coh)	1.99	(0.34, 11.67)	0.26
2	**8**	**W. Europe**	**PERS, SVEN**	**1.22**	**(0.84, 1.76)**	**0.19**
3		W. Europe	LEE	1.17	(0.84, 1.64)	0.22
3	**11**	**China**	**GAO**	**1.19**	**(0.87, 1.62)**	**0.19**
4		China	GENG, LIU, WUWI	0.95	(0.80, 1.12)	0.70

[1] Each line contains the studies in the previous tiers plus those added.
[2] Percent of total weight for Tier 2. Total of 102% is due to rounding.
[3] W. Europe consists of England, Scotland, and Sweden.
[4] Use of Tier 2, shown in boldface, is recommended. Tier 4 is *not* recommended.

25010319H4 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

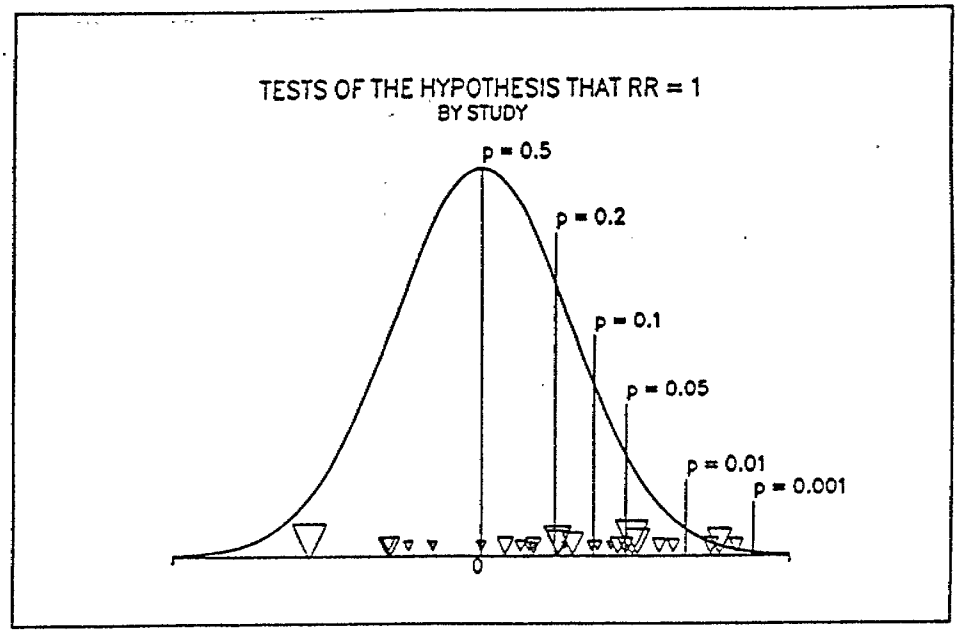


Figure 5-1. Test statistics for hypothesis RR = 1, all studies

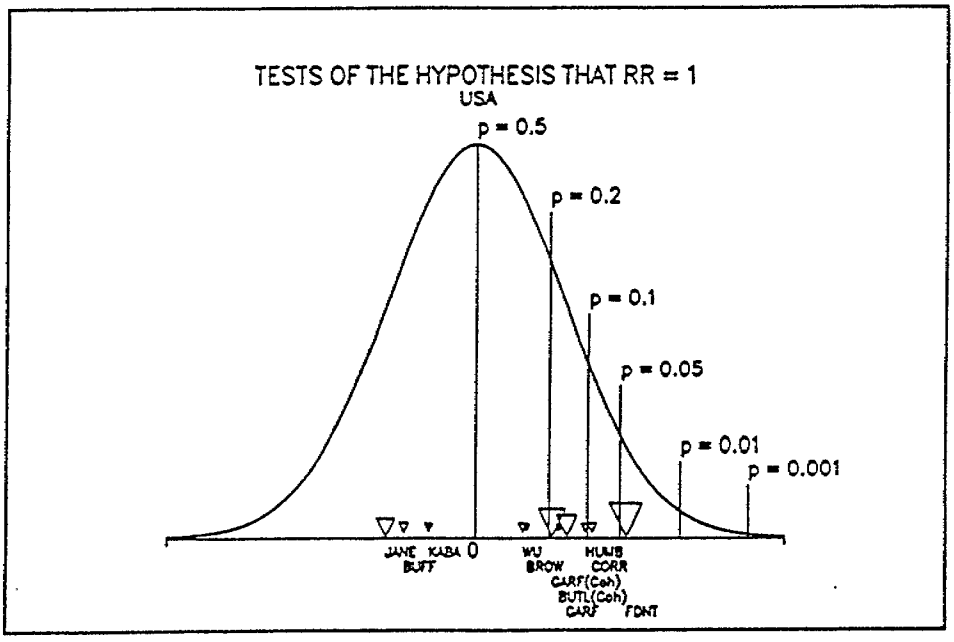


Figure 5-2. Test statistics for hypothesis RR = 1, USA only

25010319 45

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

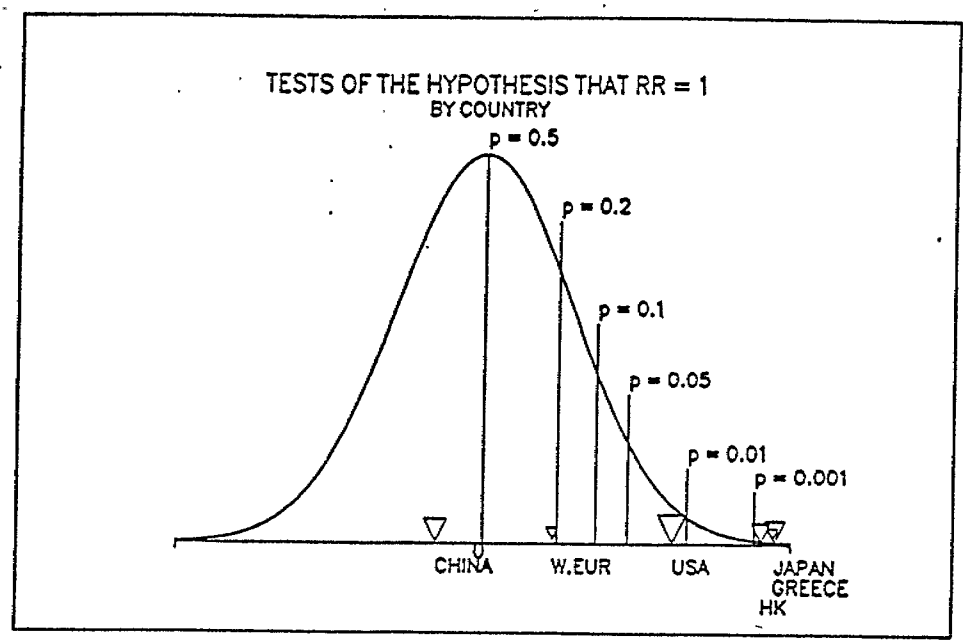


Figure 5-3. Test statistics for hypothesis RR = 1, by country

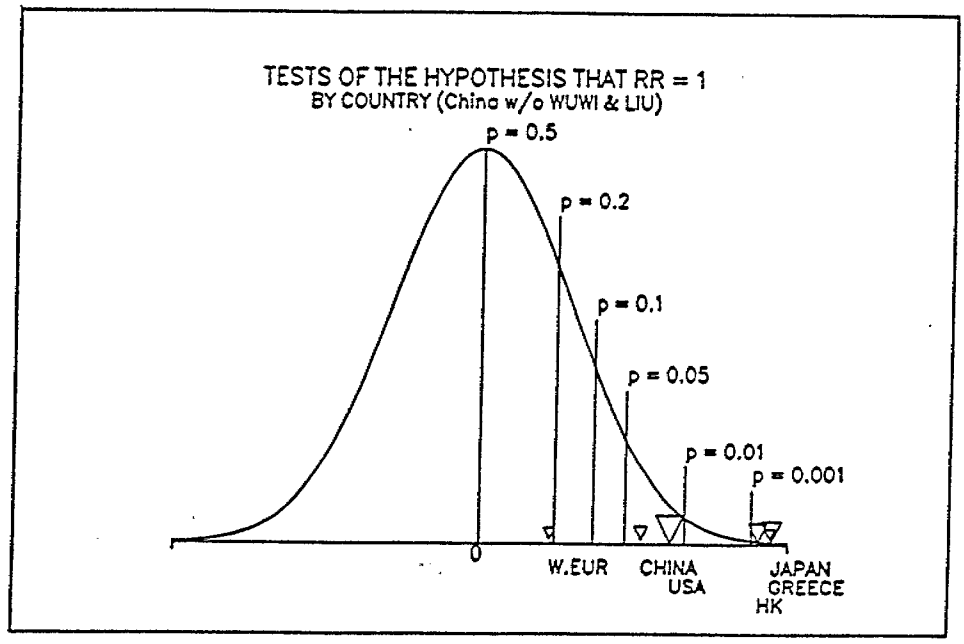


Figure 5-4. Test statistics for hypothesis RR = 1, China w/o WUWI and LIU

05/15/92
2501031946

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

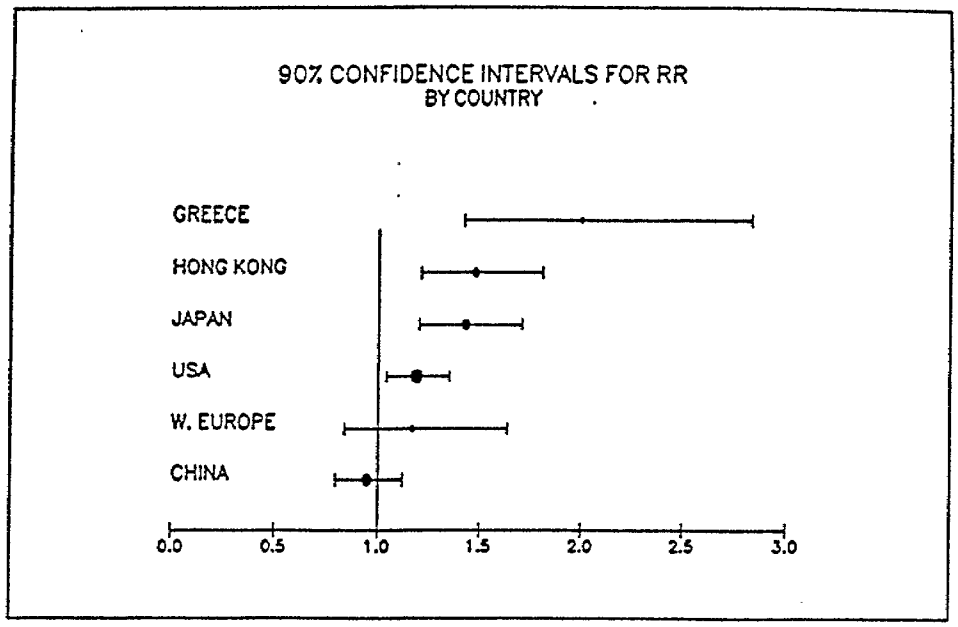


Figure 5-5. 90% confidence intervals, by country

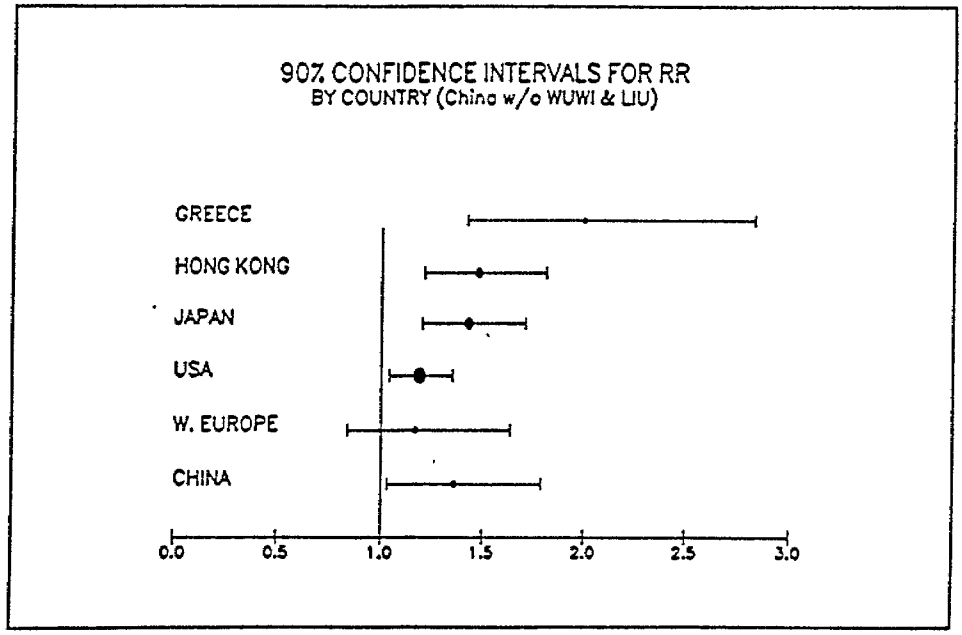


Figure 5-6. 90% confidence intervals, China without WUWI and LIU

250103194?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

6. POPULATION RISK OF LUNG CANCER FROM PASSIVE SMOKING

6.1. INTRODUCTION

The preceding chapter addressed the topic of hazard identification and concluded that environmental tobacco smoke (ETS) exposure is causally associated with lung cancer. If an effect is large enough to detect in epidemiologic studies investigating the consequences of ETS exposure at common exposure levels, the individual risk associated with exposure is considered to be high compared to most environmental contaminants assessed. Of course, the number of lung cancer deaths attributable to ETS exposure for a whole population, such as the United States, depends on the number of persons exposed as well as the individual risk. Studies of cotinine/creatinine concentrations in nonsmokers indicate that ETS is ubiquitous. For example, in urinary bioassays of 663 nonsmokers, Cummings et al. (1990) found that over 90% had detectable levels of cotinine. Among the 161 subjects who reported no recent exposure to ETS, the prevalence of detectable cotinine was still about 80%. Although the average cotinine level for all those tested may be below the average for subjects exposed to spousal ETS, as studied in this report, it indicates uptake of ETS to some extent by a large majority of nonsmokers (see also Chapter 3). Consequently, exposure to ETS is a public health issue that needs to be considered from a national perspective.

This chapter derives U.S. lung cancer mortality estimates for female and male never-smokers and long-term (5+ years) former smokers. Section 6.2 discusses prior approaches to estimating U.S. population risk. Section 6.3 presents this report's estimates. First, the parameters and formulae used are defined (Section 6.3.2), and then lung cancer mortality estimates are calculated from two different data sets and confidence and sources of uncertainty in the estimates are discussed. Section 6.3.3 derives estimates based on the combined relative risk estimates of the 11 U.S. studies from Chapter 5. Section 6.3.4 bases its estimates on the data from the single largest U.S. study, that of Fontham et al. (1991). Finally, Section 6.3.5 discusses the sensitivity of the estimates to changes in various parameter values. ETS-attributable lung cancer mortality rates for each of the individual studies from Chapter 5 are presented in Appendix D.

6.2. PRIOR APPROACHES TO ESTIMATION OF POPULATION RISK

Several authors have estimated the population risk of lung cancer from exposure to ETS previously. Two approaches have been used almost exclusively. One approach analyzes the overall epidemiologic evidence available from case-control and cohort studies, as done in this report; the other estimates a dose-response relationship for ETS exposure extrapolated from active

250103194B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

smoking, based on "cigarette-equivalents" determined from a surrogate measure of exposure common to passive and active smoking. A recent review of risk assessment methodologies in passive smoking may be found in Repace and Lowrey (1990).

6.2.1. Examples Using Epidemiologic Data

The National Research Council report (NRC, 1986) is a good example of the epidemiologic approach. An overall estimate of relative risk (RR) of lung cancer for never-smokers exposed to both and spousal smoking and background ETS versus those exposed only to background ETS is obtained by statistical summary across all available studies. Two "corrections" are then made to the estimate of RR to correct for the two sources of systematic bias. The first correction accounts for expected upward bias from former smokers and current smokers who may be misclassified as never-smokers; this correction results in a decrease in the RR estimate. The second correction is an upward adjustment to the RR taking into account the risk from background exposure to ETS (experienced by a never-smoker whether married to a smoker or not) to obtain estimates of the excess lung cancer risk from all sources of ETS exposure (spousal smoking and background ETS) relative to the risk in an ETS-free environment. Population risk can then be characterized by estimating the annual number of lung cancer deaths among never-smokers attributable to all sources of ETS exposure. This calculation requires the final corrected estimates of relative risk (one for background ETS only and one for background plus spousal smoking), the annual number of lung cancer deaths (LCDs) from all causes in the population assessed (e.g., never-smokers of age 35 and over), and the proportion of that population exposed to spousal smoking. The entire population is assumed to be exposed to some average background level of ETS; although, in fact, the population contains some individuals with high exposure and others with virtually no exposure.

The NRC report combines data for female and male never-smokers to obtain an overall observed RR estimate of 1.34 (95% C.I. = 1.18-1.53), but this estimate is most heavily influenced by the abundant female data. (The female data alone generate a combined RR estimate of 1.32 [95% C.I. = 1.18-1.52], while the male data produce an RR estimate of 1.62 [95% C.I. = 0.99-2.64].) To adjust for potential misclassification bias, the NRC uses the construct of Wald and coworkers. The technical details of the adjustment are contained in Wald et al. (1986) and to a lesser degree in the NRC report. After correcting the overall observed RR estimate of 1.34 downward for an expected positive (upward) bias from smoker misclassification, the NRC concludes that the relative risk is about 1.25, and probably lies between 1.15 and 1.35. Correction for background sources (i.e., nonspousal sources of ETS) increases the NRC estimate of RR for an

2501031949

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

"exposed" person (i.e., exposed to ETS from spousal smoking) to 1.42 (range of 1.24 to 1.61); the change is due only to implicit redefinition of RR to mean risk relative to zero-ETS exposure instead of relative to nonspousal sources of ETS. Under this redefinition, the RR for an "unexposed" person (i.e., unexposed to spousal ETS) versus a truly unexposed person (i.e., in a zero-ETS environment) becomes 1.14 (range of 1.08 to 1.21). The NRC report further estimates that about 21% of the lung cancers in nonsmoking women and 20% in nonsmoking men may be attributable to exposure to ETS (NRC, 1986, Appendix C); these estimates, however, are based on RRs corrected for background ETS but not for smoker misclassification. Applying these percentages to estimates of 6,500 LCDs in never-smoking women and 3,000 LCDs in never-smoking men in 1988 (American Cancer Society, personal communication), the number attributable to ETS exposure is 1,365 and 600, respectively, for a total of about 2,000 LCDs among never-smokers of both sexes.

Robins (NRC, 1986--Appendix D [included in the NRC report but neither endorsed nor rejected by the committee]) explores three approaches to assessment of lung cancer risk from exposure to ETS, each with attendant assumptions clearly stated. A related article by Robins et al. (1989) contains most of the same information. Method 1 is based solely on evaluation of the epidemiologic data applying two assumptions: (1) correction of relative risk for background exposure to ETS independent of age, and (2) the excess relative risk in a nonsmoker is proportional to the lifetime dose of ETS. In this method, Robins uses a weighted average RR of 1.3. After correcting this RR for background ETS exposure, age-adjusted population-attributable risks are calculated for females and males separately. Adjusting Robins' results to 6,500 annual LCDs in female never-smokers and 3,000 LCDs in male never-smokers, for comparison purposes, yields estimates of 1,870 female LCDs and 470 male LCDs attributable to ETS. Method 2 uses an overall relative risk value based on epidemiologic data, but also makes some assumptions to appeal to results of Day and Brown (1980) and Brown and Chu (1987) on lung cancer risk in active smokers. Again, adjusting Robins' estimates to 6,500 female LCDs and 3,000 male LCDs, the range of excess LCDs attributable to ETS is 1,650 to 2,990 for never-smoking females and 420 to 1,120 for never-smoking males. Method 3 is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

The Centers for Disease Control has published an estimate of 3,825 (2,495 female and 1,330 male) deaths in nonsmokers from lung cancer attributable to passive smoking for the year 1988 (CDC, 1991a), with reference to the NRC report of 1986. Those figures are the mid-range of values for males and females from method 2 of Robins in Appendix D of the NRC report (NRC, 1986).

2501031950

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Blot and Fraumeni (1986) published a review and discussion of the available epidemiologic studies about the same time as the Surgeon General's and the NRC reports appeared. The set of studies considered by Blot and Fraumeni are almost identical to those included in the NRC report, except for omission of one cohort study (Gillis et al., 1984), and inclusion of WU, the case-control study excluded by the NRC because the raw data were unpublished. An overall relative risk estimate calculated from the raw data for females yields 1.3 (95% C.I. = 1.1-1.5). When the results are combined for high exposure categories, the overall relative risk estimate is 1.7 (1.4-2.1).

Wells (1988) provides a quantitative risk assessment that includes several epidemiologic studies subsequent to the NRC and Surgeon General's reports of 1986 (NRC, 1986; U.S. DHHS, 1986). Like the NRC report, the epidemiologic data for both women and men are considered, for which Wells provides separate estimates of overall relative risk and attributable risk. Wells calculates an overall relative risk of 1.44 (95% C.I. = 1.26-1.66) for females and 2.1 (1.3-3.2) for males. Following the general approach of Wald et al. (1986), the misclassification percentage for ever-smokers is assumed to be 5% (compared to 7% for Wald et al.). Rates are corrected for background exposure to ETS, except in studies from Greece, Japan, and Hong Kong, where the older nonsmoking women are assumed to experience very little exposure to ETS outside the home. A refinement in the estimation of population-attributable risk is provided by adjusting for age at death (which also appears in the calculations of Robins [NRC, Appendix D]). The calculation of population-attributable risk applies to former smokers as well as never-smokers, which is a departure from Wald et al. and the NRC report. The annual number of LCDs attributable to ETS in the United States is estimated to be 1,232 (females) and 2,499 (males) for a total of 3,731. About 3,000, however, is thought to be a best current estimate (Wells, 1988). (In addition to the estimates of ETS-attributable LCDs, Wells uses the epidemiological approach to derive estimates of ETS-attributable deaths from other cancers (11,000) and from heart disease (32,000).)

Saracci and Riboli (1989), of the International Agency for Research on Cancer, review the evidence from the three cohort studies and 11 of the case-control studies (Table 4-1). The authors follow the example of the NRC and Wald et al. with respect to the exclusion of studies, and add only one additional case-control study (Humble et al., 1987). The overall observed relative risk for the studies, 1.35 (1.20-1.53), is about the same as that reported by the NRC, 1.34 (1.18-1.53). It is not reported how the overall relative risk was calculated.

Repace and Lowrey (1985) suggest two methods to quantify lung cancer risk associated with ETS. One method is based on epidemiologic data but, unlike in the previous examples discussed, Repace and Lowrey use a study comparing Seventh-Day-Adventists (SDAs) (Phillips et al., 1980a,b) with a demographically and educationally matched group of non-SDAs who are also

05/15/92
2501031951

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

never-smokers to obtain estimates of the relative risk of lung cancer mortality, in what they describe as a "phenomenological" approach. The SDA/non-SDA comparison provides a basis for assessing lung cancer risk from ETS in a broader environment, particularly outside the home, than the other epidemiologic studies. It also serves as an independent source of data and an alternative approach for comparison. Information regarding the number of age-specific LCDs and person-years at risk for the two cohorts is obtained from the study. The basis for comparison of the two groups is the premise that the non-SDA cohort is more likely to be exposed to ETS than the SDA group due to differences in lifestyle. Relatively few SDAs smoke, so an SDA never-smoker is probably less likely to be exposed at home by a smoking spouse, in the workplace, or elsewhere, if associations are predominantly with other SDAs. One of the virtues of this novel approach is that it contributes to the variety of evidence for evaluation and provides a new perspective on the topic.

Phillips et al. reported that the non-SDA cohort experienced an average lung cancer mortality rate equal to 2.4 times that of the SDA cohort. Using 1974 U.S. Life Tables, Repace and Lowrey calculate the difference in lung cancer mortality rates for the two cohorts by 5-year age intervals and then apply this value to an estimated 62 million never-smokers in the United States in 1979 to obtain a number of LCDs attributable to ETS annually. The result, 4,665, corresponds to a risk-rate of about 7.4 LCDs per 100,000 person-years. In an average lifespan of 75 years, that value equates to 5.5 deaths per 1,000 people exposed. The second method described by Repace and Lowrey is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

Wigle et al. (1987) apply the epidemiologic evidence from the SDA/non-SDA study (Phillips et al., 1980a,b) to obtain estimates of the number of LCDs in never-smokers due to ETS in the population of Canada. The estimated number of deaths from lung cancer attributable to passive smoking is calculated separately for males and females, using age-specific population figures for Canada and the age-specific rates of death from lung cancer attributable to ETS estimated by Repace and Lowrey (1985). A total of 50 to 60 LCDs per year is attributed to spousal smoking alone, with 90% of them in women. Overall, involuntary exposure to tobacco smoke at home, work, and elsewhere may cause about 330 LCDs annually.

6.2.2. Examples Based on Cigarette Equivalents

The cigarette-equivalents approach assumes that the dose-response curve for lung cancer risk from active smoking also applies to passive smoking, after extrapolation of the curve to lower doses and conversion of ETS exposure into an "equivalent" exposure from active smoking, determined from a surrogate measure of exposure common to passive and active smoking.

250103952

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Relative cotinine concentrations in body fluids (urine, blood, or saliva) of smokers versus nonsmokers and tobacco smoke particulates in sidestream smoke (SS) and mainstream smoke (MS) have commonly been used for this purpose. The lung cancer risk of ETS is assumed to equal the risk from active smoking at the rate determined by the cigarette-equivalents. For example, suppose the average cotinine concentration in exposed never-smokers is 1% of the average value found in people who smoke 30 cigarettes per day. The lung cancer risk for a smoker of (0.01)30 = 0.3 cigarettes per day is estimated by low-dose extrapolation from a dose-response curve for active smoking, and that value is used to describe the lung cancer risk for ETS exposure. This general explanation describes the nature of the approach; however, authors vary in their constructed solutions and level of detail. The basic assumption of cigarette-equivalents procedures is that the lung cancer risks in passive and active smokers are equivalently indexed by the common measure of exposure to tobacco smoke, i.e., a common value of the surrogate measure of exposure in an active and a passive smoker would imply the same lung cancer risk in both. This assumption may not be tenable, however, as MS and SS differ in the relative composition of carcinogens and other components identified in tobacco smoke and in their physicochemical properties in general; the lung and systemic distribution of chemical agents common to MS and SS are affected by their relative distribution between the vapor and particle phases, which differs between MS and SS and changes with SS as it ages; and active and passive smoking also differ in characteristics of intake, for example intermittent (possibly deep) puffing in contrast to normal (shallow) inhalation, which may affect deposition and systemic distribution of various tobacco smoke components as well.

Several authors have taken issue with the validity of the cigarette-equivalents approach. For example, Hoffmann et al. (1989), in discussing the longer clearance times of cotinine from passive smokers than from active smokers, conclude "The differences in the elimination time of cotinine from urine preclude a direct extrapolation of cigarette-equivalents to smoke uptake by involuntary smokers." A recent consensus report of an IARC panel of experts (Saracci, 1989) states "Lacking knowledge of which substances are responsible for the well established carcinogenic effect of MS, it is impossible to accurately gauge the degree of its similarity to ETS in respect to carcinogenic potential." The Surgeon General's report devotes a three-page section to the concept of cigarette-equivalents, quantitatively demonstrating how they can vary as a measure of exposure (U.S. DHHS, 1986). It concludes "These limitations make extrapolation from atmospheric measures to cigarette-equivalents units of disease risk a complex and potentially meaningless process." [On a lesser note, it has generally been assumed that the dose-response relationship for active smokers is reasonably well characterized. Recent literature raises some

2501031953

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

questions on this issue (Moolgavkar et al., 1989; Gaffney and Altshuler, 1988; Freedman and Navidi, 1987a, 1987b; Whittemore, 1988.)]

Citing cigarette-equivalents calculated in other sources, Vutuc (1984) assumes a range of 0.1 to 1.0 cigarettes per day for ETS exposure. Relative risks for nonsmokers are calculated for 10-year age intervals (40 to 80) based on the reported relationships of dose, time, and lung cancer incidence in Doll and Peto (1978). Relative risks for smokers of 0.1 to 1.0 cigarettes per day give a range in relative risk from 1.03 to 1.36. The author concludes "As it applies to passive smokers, this range of exposures may be neglected because it has no major effect on lung cancer incidence." Vutuc assumes that his figures apply to both males and females. If an exposure fraction of 75% is assumed for both males and females, the range of relative risks given correspond to a range for population-attributable risk. If the number of LCDs among never-smokers in the United States in 1988 is about 6,500 females and 3,000 males (personal communication from the American Cancer Society), then the number of LCDs in never-smokers attributable to ETS is estimated to range from 240 to 2,020 (140 to 1,380 for females alone). So Vutuc's figures are consistent with several hundred excess LCDs among never-smokers in the United States. These estimates are from our extension of Vutuc's analysis, however, and are not the claim of the author.

Repace and Lowrey (1985) describe a cigarette-equivalents approach as an alternative to their "phenomenological" approach discussed in Section 6.2.1. One objective is to provide an assessment of exposure to ETS from all sources that is more inclusive and quantitative than might be available from studies based on spousal smoking. They consider exposure to ETS both at home and in the workplace, using a probability-weighted average of exposure to respirable suspended particulates (RSP) in the two environments. Exposure values are derived from their basic equilibrium model relating ambient concentration of particulates to the number of burning cigarettes per unit volume of air space and to the air change rate. From 1982 statistics of lung cancer mortality rates among smokers and their own previous estimates of daily tar intake by smokers, the authors calculate a lung cancer risk for active smokers of 5.8×10^{-6} LCDs/year per mg tar/day per smoker of lung cancer age. The essential assumption linking lung cancer risk in passive and active smokers is that inhaled tobacco tar poses the same risk to either on a per unit basis. Extrapolation of risk from exposure levels for active smokers to values calculated for passive smokers is accomplished by assuming that dose-response follows the one-hit model for carcinogenesis. An estimated 555 LCDs per year in U.S. nonsmokers (never-smokers and former smokers) are attributed to ETS exposure (for 1980). The ratio of total LCDs in 1988 to 1980 is approximately 1.37 (Repace, 1989). With that population adjustment factor, the approximate

250103195

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

number of LCDs attributable to ETS among nonsmokers is closer to 760 for 1988 (including former smokers).

Method 3 of Robins (NRC, 1986, Appendix D--again, included in the NRC report but not specifically endorsed by the committee) extrapolates from data on active smoking, along with several assumptions. Applying his results to 6,500 females and 3,000 males, the range of excess LCDs in never-smokers due to ETS is 550 to 2,940 for females and 153 to 1,090 for males.

Russell and coworkers (1986) use data on urinary nicotine concentrations in smokers and nonsmokers to estimate exposure and risk from passive smoking. The risk of premature death from passive smoking is presumed to be in the same ratio to premature death in active smokers as the ratio of concentrations of urinary nicotine in passive to active smokers (about 0.007). Calculations are made using vital statistics for Great Britain and then extrapolated to the United States. The latter estimate, 4,000+ deaths/year due to passive smoking, is for all causes of death, not just LCDs.

Arundel et al. (1987) attributes only five LCDs among female never-smokers to ETS exposure. The corresponding figure for males is seven (both figures are adjusted to 6,500 females and 3,000 males). The expected lung cancer risk for never-smokers is estimated by downward extrapolation of the lung cancer risk/mg of particulate ETS exposure for current smokers. The authors' premise is that the lung carcinogenicity of ETS is entirely attributable to the particulate phase of ETS, and the consequent risk in passive smoking is comparable to active smoking on a per mg basis of particulate ETS retained in the lung. If the vapor phase of ETS were also considered, the number of LCDs attributable to ETS would likely increase (e.g., see Wells, 1991).

6.3. THIS REPORT'S ESTIMATES OF LUNG CANCER MORTALITY ATTRIBUTABLE TO ETS IN THE UNITED STATES

6.3.1. Introduction and Background

This report uses the epidemiologic approach because of the abundance of human data from actual environmental exposures. Furthermore, the assumptions are fewer and more valid than for the cigarette-equivalents approach. The report generally follows the epidemiologic methodology used by the NRC and others (Section 6.2.1) with three important differences. The first difference is that the NRC combined the data on females and males for its summary relative risk estimate. This report uses only the data on females because there are likely to be true sex-based differences in relative risk due to differences in exposure to background ETS and differences in background (i.e., nontobacco-smoke-related) lung cancer risk. Furthermore, the vast majority of the data are for females. The second difference is that the NRC combined study estimates of relative risk

2501031955

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

across countries for its summary relative risk estimate; this report combines relative risk estimates only within countries, and then bases the U.S. population risk assessment on the U.S. estimate only. As discussed in Chapter 5, there are apparently true differences in the observed relative risk estimates from different countries, which might reflect lifestyle differences, differences in background lung cancer rates in females, exposures to other indoor air pollutants, and differences in exposure to background levels of ETS. Therefore, for the purposes of U.S. population risk assessment, it is appropriate to use the U.S. studies; and there are far more studies currently available, so there is less need to combine across countries. The third difference is that the NRC corrected its overall estimate of relative risk downward for smoker misclassification bias. In this report the individual study estimates are corrected for smoker misclassification bias at the outset, i.e., prior to any analysis, using the particular parameters appropriate for each separate study (Appendix B).

Estimates of ETS-attributable population mortality are calculated from female lung cancer mortality rates (LCMRs), which are themselves derived from summary relative risk estimates either from the 11 U.S. studies combined (Section 6.3.3) or from the Fontham et al. (1991) study alone (Section 6.3.4), along with other parameter estimates from prominent sources (Section 6.3.2). The LCMRs in this instance are defined as the number of lung cancer deaths in 1985 per 100,000 of the population at risk. The LCMR in U.S. women under age 35 is minuscule, so only persons of age 35 and above are considered at risk. Although these LCMRs are expressed as a mortality rate per 100,000 of the population at risk, as derived they are applicable only to the entire population at risk and not to any fraction thereof that might, for example, have a different average exposure or age distribution.

The LCMR for the subpopulation and exposure scenario to which the epidemiologic studies apply most directly--never-smoking females exposed to spousal ETS--is estimated first. That estimate is then incremented to include exposure to nonspousal ETS for all never-smoking females. For the ETS-attributable population mortality estimates, these LCMRs are applied to never-smoking males and former smokers at risk, as well as to the females at risk for which the rates were specifically derived. The most reliable component of the total estimate constructed for the United States is the estimate for the female never-smokers exposed to spousal ETS. The other components require additional assumptions, which are described. As the number of assumptions increases, so does the uncertainty of the estimates. Thus, the total estimate of lung cancer risk to U.S. nonsmokers of both sexes is comprised of component estimates of varying degrees of certainty.

2501031956

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

One might argue that smokers are among those most heavily exposed to ETS, since they are in close proximity to sidestream smoke (the main component of ETS) from their own cigarettes and are also more likely than never-smokers to be exposed to ETS from other smokers. The purpose of this report, however, is to address respiratory health risks from ETS exposure in nonsmokers. In current smokers, the added risk from passive smoking is relatively insignificant compared to the self-inflicted risk from active smoking.

6.3.2. Parameters and Formulae for Attributable Risk

Several parameters and formulae are needed to calculate attributable risk. These are presented in Table 6-1, with the derivations explained below.

The size of the target population, in this case the number of women in the United States of age 35+ in 1985, is denoted by N, with $N = N_1 + N_2$, where N_1 = the number of ever-smokers and N_2 = the number of never-smokers. The total number of LCDs from all sources, T, is apportioned into components from four attributable sources: (1) nontobacco-smoke-related causes, the background causes that would persist in an environment free of tobacco smoke; (2) background ETS, which refers to all ETS exposure other than that from spousal smoking; (3) spousal ETS; and (4) ever-smoking. The risk from nontobacco-smoke-related causes (source 1) is a baseline risk (discussed below) assumed to apply equally to the entire target population (never-smokers and ever-smokers alike). The ever-smoking component of attributable risk (source 4) refers to the incremental risk above the baseline in ever-smokers (this report does not partition the incremental risk in ever-smokers further into components due to background ETS and spousal ETS, except for long-term [5+ years] former smokers). The background ETS component (source 2) is the incremental risk above the baseline in all never-smokers from exposure to nonspousal sources of ETS. The spousal ETS component (source 3) is the additional incremental risk in never-smokers exposed to spousal smoking.

The calculational formulae also require values for the parameters P_1 (prevalence of ever-smokers), P_2 (proportion of never-smokers exposed to spousal smoking), RR_1 (average lung cancer risk for ever-smokers relative to the average risk for never-smokers in the population), and RR_2 (lung cancer risk of never-smokers exposed to spousal ETS relative to never-smokers not exposed to spousal ETS). Additional parameters (RR_{11}, Z, RR_{01}, RR_{02}, and RR_{03}) are introduced or developed below.

The "baseline" risk is defined as the term in the denominator of a risk ratio. For example, in RR_1 the baseline risk is the lung cancer risk in a population of never-smokers with P_2 exposed to spousal ETS and $1-P_2$ not exposed to spousal ETS. The conversion of RR_1 to the same baseline

250103957

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

risk as RR_2 (the risk of never-smokers not-exposed to spousal ETS but still exposed to nontobacco-smoke-related causes and to background ETS), is given by

$$RR_{11} = RR_1(P_2RR_2 + 1 - P_2). \quad (6\text{-}1)$$

To convert relative risks to the baseline risk of lung cancer from nontobacco-smoke-related causes only (i.e., excluding background ETS in the baseline) requires some assumptions. Let RR_{02} denote the conversion of RR_2 to this new baseline. It is assumed that: (1) the excess risk of lung cancer from ETS exposure is proportional to ETS exposure; and (2) the ratio of ETS exposure from spousal smoking plus other sources to exposure from other sources alone, denoted by Z, is known and $Z > RR_2 > 1$ (For the values used in this document this relation is true. See also the discussion in Section 8.3). Under these assumptions, it is readily verified that

$$RR_{02} = (Z - 1)/(Z/RR_2 - 1). \quad (6\text{-}2)$$

Determination of a value for Z from data on cotinine concentrations (or cotinine/creatinine) is discussed below. The conversion of RR_1 to the same zero-ETS baseline risk as RR_{02} follows from multiplying expression (6-1) by RR_{02}/RR_2, i.e.,

$$RR_{01} = RR_1(P_2RR_{02} + (1-P_2)RR_{02}/RR_2). \quad (6\text{-}3)$$

The terms RR_{01} and RR_{02} are the lung cancer risks for ever-smokers and for never-smokers exposed to spousal ETS, respectively, relative to the risk for never-smokers in a zero-ETS environment. The risk of never-smokers not exposed to spousal ETS (but exposed to background ETS and nonsmoking causes) relative to the zero-ETS baseline risk is

$$RR_{03} = RR_{02}/RR_2. \quad (6\text{-}4)$$

The population-attributable risk of lung cancer in the total population (Levin, 1953) for a source (risk factor) is a ratio. The numerators of the ratios for sources of tobacco smoke are:

current/former active smoking in ever-smokers,
$P_1(RR_{01}-1)$; (6-5)

25010319 58

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

background ETS plus spousal ETS in never-smokers exposed to both, $(1-P_1)P_2(RR_{02}-1)$; and (6-6)

background ETS in never-smokers not exposed to spousal ETS, $(1-P_1)(1-P_2)(RR_{02}/RR_2-1)$. (6-7)

The denominator for each term is their sum plus one, i.e.,

$$Ex(6\text{-}5) + Ex(6\text{-}6) + Ex(6\text{-}7) + 1 \quad (6\text{-}8)$$

where Ex(6-5) refers to expression (6-5), etc. The population-attributable risk for remaining causes of lung cancer (nontobacco-smoke-related background causes) is

$$1/Ex(6\text{-}8). \quad (6\text{-}9)$$

Multiplying the population attributable risk for a source by the total number of LCDs yields the number of LCDs attributable to that source. Alternatively, the source-attributable LCD estimates can be derived by first calculating LCMRs. LCMRs are obtained for each source as follows:

nontobacco-smoke-related causes:	$LCMR_{nt} = 10^5 Ex(6\text{-}9)T/N.$
ever-smoking:	$LCMR_{nt}(RR_{01}-1).$
spousal ETS:	$LCMR_{nt}(RR_{02}-RR_{03}).$
background ETS:	$LCMR_{nt}(RR_{03}-1).$

Then the number of LCDs attributable to a source is estimated by multiplying the LCMR for that source by the total population at risk from that source.

We now consider parameter values for N, T, P_1, P_2, RR_1, and Z to be used with the value 1.19 for RR_2, the pooled estimate of RR_2 from the 11 U.S. studies (Table 5-17), for the population risk assessment in Section 6.3.3. The value used for RR_2 is then changed to 1.26, the estimate from the Fontham et al. study in the United States, and a new value of Z is constructed from the cotinine data in that study, for the alternative population risk assessment calculations in Section 6.3.4. The female population in 1985 of age 18+ years of age is approximately 92 million (U.S. DHHS, 1989, Chap. 3). Detailed census data by age for 1988 indicates that the proportion of women 35+ years of age in the female population of age 18+ is 0.63 (U.S. Bureau of the Census, 1990). Applying that proportion to the 1985 population gives approximately 58 million women of

2501031959

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

aged 35+ in 1985, the value used for N. There were approximately 38,000 female lung cancer deaths in the United States in 1985 (U.S. DHHS, 1989), which is used as the value for T.

Using figures from the Bureau of the Census and the 1979/80 National Health Interview Survey, Arundel et al. (1987) estimate the number of women of age 35+ by smoking status, obtaining a value of 0.443 as the fraction of ever-smokers. The National Center for Health Statistics (as reported in U.S. DHHS, 1989) provides the proportion of the female population by smoking status (never, former, current) for 1987. When applied to figures from the Bureau of the Census (1990) for the female population by age group available for 1988, the same fractional value (0.443) is obtained. These sources suggest that the proportion of ever-smokers in the female population has been fairly constant between 1980 and 1987, so P_1 will be given the value 0.443. Multiplying N by P_1 gives an estimate of $N_1 = 25.7$ million ever-smokers, leaving $N_2 = 32.3$ million never-smokers.

RR_1 applies to ever-smokers, which consist of current and former smokers. The relative risks of current and former female smokers of age 35+ for the period 1982-1986 are estimated at 11.94 and 4.69, respectively, from data in the American Cancer Society's Cancer Prevention Study II (CPS-II; as reported in U.S. DHHS, 1989). For 1985, the composition of ever-smokers is 63.4% current smokers and 36.6% former smokers (CDC, 1989). Using those percentages to weight the RRs for ever-smokers and former smokers gives 9.26, which will be used as the value of RR_1.

The proportion of never-smokers exposed to spousal ETS in epidemiologic studies typically refers to married persons, so we need to consider how to treat unmarried persons as well in order to set a value for P_2. The American Cancer Society's CPS-II (reported in Stellman and Garfinkel, 1986) percentages for marital status of all women surveyed (not just never-smokers) are: married, 75.3; divorced, 5.1; widowed, 14.6; separated, 0.8; and single, 4.2. Our estimates of risk apply to married female never-smokers, about 75% of female never-smokers, so it is necessary to consider exposure to ETS in the remaining 25% of unmarried never-smokers.

Cummings (1990) obtained urinary cotinine levels on a total of 663 self-reported never-smokers and former smokers. The cotinine levels were slightly higher in males than in females (9.6 and 8.2 ng/mL, respectively), and slightly more than one-half of the subjects were females. The average cotinine level was 10.7 ng/mL for married subjects if the spouse smoked and 7.6 ng/mL otherwise. The average cotinine levels reported by marital status are: married, 8.3 ng/mL; never married, 10.3 ng/mL; separated, 11.8 ng/mL; widowed, 10.4 ng/mL; and divorced, 9.2 ng/mL. The study, in which 7% of the subjects were of age 18 to 29, and 47% were of age 60 to 84, does not claim to be representative. Nevertheless, the results suggest that in terms of ETS exposure, an unmarried never-smoker is probably closer, on average, to a never-smoker married

2501031960

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

to a smoker (an exposed person) than to a never-smoker married to a nonsmoker (an unexposed person). This observation is also consistent with the findings of Friedman et al. (1983).

The proportion of never-smoking controls exposed to spousal smoking varies among studies in the United States. If we exclude studies of uncertain representativeness (entered in Table 5-14A under "representativeness"), the median value for the remaining studies is 0.6. From the evidence on ETS exposure to unmarried female never-smokers, it is reasonable to assume that their exposure to ETS, on average, is at least as large as the average background level plus 60% of the average exposure from spousal smoking. For the calculations needed from these figures, this assumption is equivalent to treating unmarried and married female never-smokers alike, in terms of exposure to ETS (i.e., 60% exposed at a level equivalent to spousal smoking plus background and 40% exposed at the background level only). Consequently, the value $P_2 = 0.6$ is assumed to apply equally to married and unmarried female never-smokers.

The NRC report of 1986 uses Z = 3 for the ratio of ETS exposure from spousal smoking plus other sources to ETS exposure from nonspousal sources alone. That value was primarily based on data from Wald and Ritchie (1984), for men in Great Britain, although Lee (1987b) had reported a value of 3.3 for women in Great Britain. The results of Coultas et al. (1987) were also considered, wherein a value of 2.35 was observed for saliva cotinine levels in a population-based survey of Hispanic subjects in New Mexico. More recent data suggest that a lower value of Z may be more accurate for the United States. The study of 663 volunteers in Buffalo, New York, reported by Cummings et al. (1990), observed a value of 1.55 based on mean urinary cotinine levels among married females (n = 225; Cummings, 1990). A study by Wall et al. (1988) containing 48 nonsmokers observed a ratio of mean cotinine levels of 1.53. A survey of municipal workers at a health fair found a cotinine ratio of 2.48 for the 112 women surveyed, but the comparison is between women who shared living quarters with a smoker and those who did not (Haley et al., 1989). The 10-country collaborative cotinine study conducted by IARC (Riboli, 1990) collected urinary cotinine samples from nonsmoking women in four groups totaling about 100 each--married to a smoker (yes, no) and employed (yes, no)--including two locations, Los Angeles and New Orleans, in the continental United States. The ratios of average cotinine/creatinine concentrations for women married to a smoker to women not married to a smoker range from 1.75 to 1.89 in New Orleans, when the percentage of women employed is assumed to be between 25% and 75%. The data from Los Angeles contain an abnormally high mean for women who are employed and also married to a smoker (a mean of 14.6 based on only 13 observations, compared to the other three means for Los Angeles of 2.1, 4.5, and 6.6), so only the two means for unemployed women (married to a smoker and married to a nonsmoker) were

250103196

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

used. The resultant ratio of cotinine/creatinine concentrations is 1.45. Data from the Fontham et al. (1991) study of lung cancer and ETS exposure in five U.S. cities yield a Z of 2.0 based on mean urinary cotinine levels in 239 never-smoking women (data provided by Dr. Elizabeth Fontham).

Cotinine data exhibit variability both within and between subjects, as well as between studies due to different experimental designs, protocols, and geographical locations (see also Chapter 3). The Z values from recent U.S. studies mostly range between 1.55 and 2.0. A value of 1.75 for Z appears reasonable based on the available U.S. data and will be used in Section 6.3.3 along with the combined RR estimate from 11 U.S. studies (Chapter 5) to calculate ETS-attributable lung cancer mortality estimates. Z = 2.0 and Z = 2.6, which is based on *median* cotinine levels, will be used in Section 6.3.4 for alternative calculations of lung cancer mortality based on the results of the Fontham et al. (1991) study. The sensitivity of the lung cancer mortality estimates to changes in Z and other parameters is discussed in Section 6.3.5.

6.3.3. U.S. Lung Cancer Mortality Estimates Based on Results of Combined Estimates from 11 U.S. Studies

This section calculates ETS-attributable U.S. lung cancer mortality estimates based on the combined relative risk estimate (RR_2 = 1.19) derived in Chapter 5 for the 11 U.S. studies. Alternatively, the estimate from just the combined Tier 1 and Tier 2 studies (RR_2 = 1.19 from 6 of the 11; see Table 5-17) could have been used since these six studies were assessed as having the greater utility in terms of evaluating the lung cancer risks from ETS; however, the results would be virtually the same since all that differs from these combinations is the confidence interval on the relative risk. It was therefore decided to use the data from all the U.S. studies for the purposes of the population risk assessment.

6.3.3.1. *U.S. Lung Cancer Mortality Estimates for Female Never-Smokers*

The parameter values presented in Section 6.3.2 are assumed along with RR_2 = 1.19. For Z = 1.75, RR_{02} = 1.59 (from expression 6-2, denoted hereafter as Ex(6-2); see also Table 6-1). Given those parameter values, the formulae in Section 6.3.2 yield the estimated lung cancer mortality for U.S. women in 1985 by smoking status (ever-smoker, never-smoker exposed to spousal ETS, and never-smoker not exposed to spousal ETS) and source (nontobacco-smoke-related causes, background ETS in never-smokers, spousal ETS in never-smokers, and ever-smoking), as displayed in Table 6-2. The lung cancer mortality rate from nontobacco-smoke-related causes ($LCMR_{nt}$) is estimated to be 9.4 per 100,000, and is assumed to apply equally to all persons in the target population, regardless of smoking status. The excess LCMR in never-

250103196?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

smokers from exposure to background ETS is 3.2, with an additional 2.4 if exposed to spousal ETS. The excess LCMR in ever-smokers, which includes whatever effect exposure to ETS has on ever-smokers as well as the effect from active smoking, is 120.8.

In rounded figures, 5,470 (14.4%) of the 38,000 LCDs in U.S. women of age 35+ in 1985 are unrelated to smoking (active or passive). The remaining 32,530 lung cancer deaths (85.6% of the total) are attributable to tobacco smoke: 31,030 in 25.7 million ever-smokers and 1,500 in 32.3 million never-smokers. These 1,500 ETS-attributable LCDs in never-smokers account for about one-third of all lung cancer deaths in female never-smokers. Of the 1,500 LCDs, about 1,030 (69%) are due to background ETS, and 470 (31%) are from spousal ETS. In summary, the total 38,000 LCDs from all causes is due to: nontobacco-smoke-related causes, 5,470 (14.4%), occurring in ever-smokers and never-smokers; ever-smoking, i.e., the effects of past and current active smoking as well as ETS exposure, 31,030 (81.7%), occurring in ever-smokers; background ETS, 1,030 (2.7%), and spousal ETS, 470 (1.2%), occurring in never-smokers. In other words, ever-smoking causes about 81.7% of the lung cancers in women of age 35+; exposure to ETS from all sources accounts for some 3.9%; and causes unrelated to tobacco smoke are responsible for the remaining 14.4%. The LCDs in never-smokers attributable to ETS equal about 5% (1,500/31,030) of the total attributable to ever-smoking. Part of the mortality attributed to ever-smoking here, however, is due to ETS exposure in former smokers, to be taken into account in Section 6.3.3.3.

6.3.3.2. *U.S. Lung Cancer Mortality Estimates for Male Never-Smokers*

There are 11 studies of exposure to ETS and lung cancer in males. The studies and their respective relative risks are AKIB, 1.8; BROW, 2.2; BUFF, 33+ years exposure, 1.6; CORR, 2.0; HUMB, 4.2; KABA, 1.0; LEE, 1.3; HIRA(Coh), 2.25; HOLE(Coh), 3.5; plus the data in Kabat (1990), 1.2; and Varela (1987, Table 13 scaled down to 50 years of exposure), 1.2. (Data for BROW, BUFF, and HUMB were supplied via personal communication from Drs. Brownson, Buffler, and Humble). A weighted average of the passive smoking risk (RR_2) from these 11 studies is about 1.6. For the seven U.S. studies, BROW, BUFF, CORR, HUMB, KABA, Kabat (1990), and Varela (1987), the weighted average RR is about 1.4, but this value is heavily weighted (about 66%) by the Kabat (1990) and Varela studies, neither of which was used in the analysis of the female data. The combined risk for the five U.S. studies not including Kabat (1990) and Varela is about 1.8, but they are all small, low-weight studies. In any case the observed relative risks for males appear to be at least as great as those for females.

When an attempt is made to correct the observed male risks for smoker misclassification, however, using the procedures outlined in Appendix B and the community survey-based

25010319 63

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

misclassification factors for males (1.6% for current regular smokers, 15% for current occasional smokers, and 5.9% for former smokers), it is found that for most of these cohorts, the number of smokers misclassified as never-smokers either exceeds the relatively small number of observed never-smokers, or is so great as to drive the corrected relative risk substantially below unity. This implies that the misclassification factors from the community surveys are too high to accurately correct the risks in the epidemiologic studies. Until better misclassification data on males are available, no real sense can be made of the male passive smoking relative risks.

Under these circumstances, it was decided to apply the incremental LCMRs for spousal and nonspousal ETS exposure in female never-smokers to male never-smokers. The incremental LCMRs were used instead of the relative risk estimates because relative risk depends on the background risk of lung cancer (from nontobacco-related causes) as well as the risk from ETS, and background lung cancer risk may differ between females and males. From Section 6.3.3.1, the LCMR from spousal ETS exposure was 2.4 per 100,000 at risk, and the LCMR from nonspousal ETS exposure was 3.2 per 100,000. The 1985 male population age 35 and over is 48 million (U.S. DHHS, 1989) of whom 27.2% (private communication from Dr. Ronald W. Wilson of the U.S. National Center for Health Statistics), or 13.06 million, were never-smokers. Of these, 24% (Wells, 1988), or 3.13 million, were spousally exposed. Applying the female ETS LCMRs, 3.13 million x 2.4/100,000 = 80 deaths in males from spousal ETS exposure and 13.06 million x 3.2/100,000 = 420 deaths from nonspousal exposure, for a total of 500 ETS-attributable LCDs among never-smoking males. These estimates based on female LCMRs are believed to be conservatively low because males generally have higher exposure to background ETS than females. This would lead to lower Z values and subsequently higher estimates of deaths attributable to background (nonspousal) ETS sources. In conclusion, confidence in these estimates for male never-smokers is not as high as in those for female never-smokers.

6.3.3.3. *U.S. Lung Cancer Mortality Estimates for Long-Term (5+ Years) Former Smokers*

There is a scarcity of data on the relative risks of lung cancer for former smokers exposed to ETS. With former smokers, it would be difficult to know how much of the observed lung cancer mortality is attributable to nontobacco-smoke-related causes, how much is due to ETS exposure, and how much is accounted for by prior smoking. Consequently, observational data on the number of lung cancers in former smokers are not utilized. Instead, long-term former smokers are assumed to have the same lung cancer mortality rate from exposure to ETS as never-smokers. Assuming that the residual excess risk of lung cancer from active smoking largely diminishes in about five years, this analysis treats former smokers who have quit for less than

250103196

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

5 years the same as current smokers and those who have quit for longer periods the same as never-smokers. Varela (1987) studied the relative risk for lung cancer from ETS exposure in 242 long-term (10+ years) former smokers. He found that for total household exposure to ETS there was very little difference between the relative risks for these long-term former smokers and the never-smokers (see, for example, his Tables 12 and 13). There is still some uncertainty in the application of these assumptions because the risk to long-term former smokers may not, in fact, be the same as the risk to never-smokers. For example, ETS may have an additional promotional effect on former smokers because of their previous exposures to high concentrations of carcinogens from active smoking.

Female ever-smokers comprise about 44.3%, or 25.7 million, of the total U.S. female population, age 35 and over, of 58 million. Long-term (5+ years) former smokers comprise about 34% of these ever-smokers (U.S. DHHS, 1990) or about 8.7 million. Using a 2.2 concordance factor for former smokers married to ever-smokers versus never-smokers married to never-smokers (See Appendix B), it is estimated that about 77% of the former smokers, or about 6.7 million, would be spousally exposed compared with the 60% for the never-smokers. Thus, based on the LCMRs derived for female never-smokers, the expected number of ETS-attributable LCDs for female long-term former smokers would be 6.7 million x 2.40/100,000 = 160 deaths from spousal exposure and 8.7 million x 3.20/100,000 = 280 deaths from nonspousal exposure, for a total of 440.

Male ever-smokers comprise 72.8% of the U.S. male population, age 35 and over, of 48 million equal to 35 million of whom about 43% (derived from data in U.S. DHHS, 1990, page 60, Table 5), or about 15 million, are 5+ year quitters. Of the never-smoking males, 24% were married to smokers (Section 6.3.3.2). Again using a 2.2 concordance factor for former smokers, it is estimated that 41% of the 15 million former smoking males, or 6.2 million, would be married to ever-smokers. Applying the female never-smoker LCMRs from Section 6.3.3.1, 6.2 million x 2.40/100,000 = 150 deaths from spousal ETS exposure and 15 million x 3.20/100,000 = 480 deaths from nonspousal ETS exposure for a total of 630 ETS-attributable LCDs among male long-term former smokers.

Table 6-3 displays the resultant estimates for LCDs attributable to background ETS and spousal ETS, for never-smokers and for former smokers who have quit for at least five years, by sex. The LCMRs for background ETS and spousal ETS, assumed to be independent of smoking status and sex, are the same as derived in Section 6.3.3.1 for females never-smokers (3.2 and 2.4, respectively). Background ETS accounts for about 2,200 (72%) and spousal ETS for 860 (28%) of the total due to ETS. Of the 3,060 ETS-attributable LCDs, about two-thirds are in females

05/15/92
250103196

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

(1,930; 63%) and one-third in males (1,130; 37%). More females are estimated to be affected because there are more female than male never-smokers. By smoking status, two-thirds are in never-smokers (2,000; 65%) and one-third in former smokers who have quit for at least 5 years (1,060; 35%).

The numbers shown in Table 6-3 depend, of course, on the parameter values assumed for the calculations. The sensitivity of the totals in Table 6-3 to alternative parameter values is addressed in Section 6.3.5. First, however, tables equivalent to Tables 6-2 and 6-3 are developed based on the FONT study alone, for comparison.

6.3.4. U.S. Lung Cancer Mortality Estimates Based on Results of the Fontham et al. (1991) Study (FONT)

The estimate of RR_2 (1.19), the risk of lung cancer to female never-smokers with spousal ETS exposure relative to the risk for female never-smokers without spousal ETS exposure, used in Section 6.3.3, is based on the combined outcomes of the 11 U.S. epidemiologic studies from Chapter 5 (see Table 5-17). In this section the quantitative population impact assessment is repeated with FONT, the single U.S. study with Tier 1 classification (Section 5.4.4), as the source of the estimates of RR_2 and Z (constructed from urine cotinine measures), with the remaining parameter values left unchanged. While a single study has lower power and larger confidence intervals on the relative risk estimate than can be obtained by combining the various U.S. studies, using the specific data from a single study decreases the uncertainties inherent in combining results from studies that are not fully comparable. FONT is the only study of passive smoking and lung cancer that collected cotinine measurements, thus providing estimates for RR_2 and Z from a single study population. The total number of lung cancers attributable to total ETS exposure is particularly sensitive to those two parameters (discussed in Section 6.3.5).

The NCI-funded Fontham et al. study (1991) is a large, well-conducted study designed specifically to investigate lung cancer risks from ETS exposure (see also the critical review in Appendix A). It addresses some of the methodological issues that have been of concern in the interpretation of results regarding lung cancer and passive smoking: smoker misclassification, use of surrogate respondents, potential recall bias, histopathology of the lung tumors, and possible confounding by other factors (see also Sections 5.3, 5.4.2 and 5.4.3). Cases and controls were drawn from five major cities across the United States (Atlanta, New Orleans, Houston, Los Angeles, and San Francisco) and, hence, should be fairly representative of the general U.S. population, at least of moderate climate urban areas. Furthermore, the results of the study are consistent across the five cities.

250103196

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

In spite of the care incorporated into the FONT design to avoid smoker misclassification bias, some might still exist; thus, the adjusted relative risk of 1.29 reported in FONT is "corrected" slightly to 1.26 in this report. The parameter P_2, the proportion of never-smokers exposed to spousal ETS, was assigned the value 0.60 in the preceding section. In FONT, the observed proportion of spousal-exposed controls is 0.60 (0.66) for spousal use of cigarettes only (any type of tobacco) among colon-cancer controls and 0.56 (0.63) in population controls. Consequently, the previous value of 0.60 is retained. Of the 669 FONT population controls, whose current cotinine levels are considered the most representative of typical ETS exposure, there were 59 living with a current smoker and 239 whose spouses never smoked. (The other 371 were nonsmoking women who either no longer lived with a smoking spouse or whose spouse was a former smoker.) The *mean* cotinine level for never-smoking women with spouses who are current smokers (n = 59) is 15.90 ± 16.46; the mean level for the other 239 was 7.97 (± 11.03). The ratio is 15.90/7.97, giving Z = 2.0 (data provided by Dr. Elizabeth Fontham). The median is a measure of central tendency that is less sensitive to extremes, so the ratio of *median* cotinine levels is also considered (Z = 11.4/4.4 = 2.6). Results for both values of Z are displayed in Tables 6-4 and 6-5, which correspond to Tables 6-2 and 6-3, respectively, of the previous sections for direct comparison.

The results of Section 6.3.2 are based on RR_2 = 1.19 (combined U.S. study results) and Z = 1.75 (from studies on cotinine levels). In this section, RR_2 and Z are both increased (RR_2 to 1.26 and Z to 2.0 and 2.6). The change in RR_2 increases the estimated number of LCDs from background and spousal ETS, while increasing Z decreases the figure for background ETS and has no effect on the number for spousal ETS (see Tables 6-2 and 6-4). Relative to the total for ETS in the last section (3,060), the net effect is an increase of 8% to 3,300 at Z = 2.0 and a decrease of 19% to 2,480 when Z = 2.6. Subject to the accuracy of the parameter values assumed, these two analyses support an estimate in the neighborhood of 3,000 total lung cancer deaths in never-smokers and former smokers (quitters of 5+ years) from exposure to ETS in the United States for 1985.

The 3,000 figure is a composite value from estimates of varying degrees of uncertainty. The confidence for the never-smoker estimates is highest. Comparing Tables 6-2 and 6-4 for never-smokers, the lung cancer estimates for never-smoking females from exposure to spousal ETS (470 - 610) are based on the direct evidence from epidemiologic studies and require the fewest assumptions. Adding in a figure for exposure to background ETS in never-smoking females (640 - 1,030) is subject to the assumptions and other uncertainties attached to the estimate of the parameter Z. The relative risk from ETS exposure, which depends on the risk from background sources of lung cancer as well as the risk from ETS, may differ in females and males.

2501031967

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Consequently, the absolute risk (LCMR) in females was assumed to apply to males, adding 360 - 510 to the total (80 - 100 for spousal ETS and 260 - 420 for background ETS; Table 6-3 and 6-5). Males, however, are thought to have higher background exposures to ETS than females, so this assumption is likely to underestimate the ETS-attributable lung cancer mortality in males. Also, there is uncertainty attached to the number of male never-smokers and the proportion exposed to ETS, which affect the figures for males.

The confidence in the estimates for former smokers is less than in those for never-smokers. The estimates are probably low since they assume that ETS-attributable rates in never-smokers and former smokers are the same. Figures for lung cancer mortality from ETS in former smokers, for the same categories as never-smokers (i.e., females and males, background and spousal ETS) account for an additional 870 - 1,160 (totals of 310 - 410 for spousal ETS and 470 - 760 for background ETS, for both sexes). These figures for former smokers are summed from appropriate entries in Tables 6-3 and 6-5 (Tables 6-2 and 6-4 do not make them explicit; they are accounted for in the entry for lung cancer attributable to ever-smoking).

FONT is the largest study and therefore the dominant influence in the combined relative risk from the 11 U.S. studies (RR_2 = 1.19), so the outcomes being compared here with those in Section 6.3.3 are not independent. Similarly, the Z-value of 1.75 used with RR_2 = 1.19 in the first analysis is subjectively based on the outcomes of several U.S. cotinine studies, including the FONT cotinine results. It is already apparent that the estimate of total lung cancer mortality attributable to ETS is sensitive to the values of Z and RR_2. Uncertainties associated with the parameter values assumed and the sensitivity of the estimated total ETS-attributable LCDs to the various parameter values are examined next.

6.3.5. Sensitivity to Parameter Values

The estimates for ETS-attributable lung cancer mortality are clearly sensitive to the studies, methodology, and choice of models used, and previous methodologies have been presented in Section 6.2. Even for this current model, however, estimates will vary with different input values. Specifically, the estimates depend on the parameter values assumed for the total number of lung cancer deaths from all sources (T), the population size (N), the proportion of ever-smokers in the population (P_1), the proportion of never-smokers exposed to spousal ETS (P_2), the risk of ever-smokers relative to never-smokers (RR_1), the risk of never-smokers exposed to spousal ETS relative to unexposed never-smokers (RR_2), and the ratio of ETS exposure from spousal smoking and background (i.e., nonspousal) sources to background sources alone (Z).

2501031968

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The effects of changing several of the parameters is readily discernible. A change in T/N produces a proportional change in the same direction for all estimates of attributable mortality. A change in P_1 creates a proportional change in the same direction in all mortality figures for ever-smokers and a change in the opposite direction proportional to 1 - P_1 in all estimates for never-smokers. The parameter values assumed for these three parameters are from the sources described in the preceding text and are assumed to be acceptably accurate. The value of P_2 is assumed to be 0.6, but values between 0.5 and 0.7 are easily credible. At either of those extremes, there is a 17% change in the lung cancer mortality due to spousal smoking, which only amounts to 80 for the first analysis (Table 6-2) and 100 for the second one (Table 6-4). The impact of changing RR_1, RR_2, or Z on the total lung cancer mortality attributable to ETS from the first analysis is displayed in Table 6-6 for RR_1 from 8 to 11, RR_2 between 1.04 and 1.35 (extremes of the 90% confidence intervals for the 11 U.S. studies; Table 5-17) and for Z in the range 1.5 to 3.0.

For RR_1 in the interval (8,11), the total lung cancer mortality from ETS ranges from about 2,600 to 3,500, a 14% change in either direction relative to the comparison total of 3,060. The extremes are much greater over the range of values considered for RR_2 (1.04 to 1.35). At the low end, where the excess relative risk from spousal ETS is only 4%, there is an 77% decrease in the total lung cancer mortality to 700. The percentage change is roughly equivalent in the opposite direction when the excess relative risk is at the maximum value 35%, for a total of 5,190. The total is also sensitive to the value of Z. A decrease of only 0.25 from the comparison value of 1.75 increases the total by 36% to 4,160. A 36% decrease occurs at 2.5, leaving a corresponding estimate of 1,950. At Z = 3.0, the total drops further to 1,680, a 45% decrease. Clearly, there are fairly large swings in the estimated total number of lung cancer deaths attributable to ETS from varying RR_2 or Z by itself.

Varying more than one parameter value simultaneously may have a compounding or canceling effect on the total lung cancer mortality due to ETS. For example, at the following values of RR_2, the range of percentage changes from the total of 3,060 ETS-attributable lung cancer deaths for values of Z in the interval 1.50 to 3.0 are shown in parentheses: RR_2 = 1.04 (-69%, -88%), RR_2 = 1.15 (+10%, -56%), RR_2 = 1.25 (+73%, -30%), and RR_2 = 1.35 (+131%, -7%). The total ETS-attributable LCD estimates range from 380 (at RR_2 = 1.04, Z = 3.0) to 7,060 (at RR_2 = 1.35, Z = 1.5). Without considering the additional variability that other parameters might add, it is apparent that the estimated lung cancer mortality from ETS is sensitive to the parameters RR_2 and Z, and that the uncertainty in these parameters alone leaves a fairly wide range of possibilities for the true population risk.

2501031969

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

While various extreme values of these parameters can lead to the large range of estimates noted, the extremities of this range are less likely possibilities for the true population risk because the parameters RR_2 and Z are not actually independent and would be expected to co-vary in the same direction, not in the opposite direction as expressed by the extreme values. For example, if the contributions of background ETS to total exposure decrease, Z would increase, and the observable relative risk from spousal exposure, RR_2, would be expected to increase as well. Furthermore, most of the evidence presented in this report suggests that a narrower range of both RR_2 and Z are appropriate. Thus, while variations are possible, this report concludes that the estimate of approximately 3,000 ETS-attributable LCDs based on the 11 U.S. studies is a reasonable one, with the population risk analysis based on FONT providing a fairly reliable range--2,500 to 3,300 ETS-attributable LCDs.

6.4. SUMMARY AND CONCLUSIONS ON POPULATION RISK

Having concluded in the previous chapter that ETS is a cause of lung cancer in humans and belongs in EPA Group A of carcinogens, this chapter assesses the magnitude of that health impact in the U.S. population. The ubiquity of ETS in a typical individual's living environment results in the respiratory uptake of tobacco smoke to some degree in a very high percentage of the adult population, conservatively upwards of 75% based on the outcome of cotinine/creatinine studies in nonsmokers. Compared to observations on active smokers, urinary cotinine in nonsmokers is small, on the order of a few percent, and there is considerable variability in inter-individual metabolism of nicotine to cotinine. Some authors have used the relative cotinine levels in active and passive smokers to estimate the probability of lung cancer in nonsmokers, by extrapolating downward on a dose-response curve for active smokers. This "cigarette-equivalents" approach requires several assumptions, e.g. that the dose-response curve used for active smokers is reasonably accurate and low-dose extrapolation of risk for active smokers is credible, that cotinine is proportional (and hence a substitute for) whatever is used for "dose" in the dose-response curve, and that the risk calculated in this way applies equally to active and passive smokers with equivalent cotinine measures. The effect of differences in physico-chemical properties of mainstream smoke and sidestream smoke (the principal component of ETS), in lung dosimetry between active and passive smoking, and in exposure patterns (related to concentration and duration of exposure) are not fully understood, but the current state of knowledge casts doubts on the validity of these assumptions.

The remaining approach to population risk extrapolates to the general population from the epidemiologic evidence of increased relative risk of lung cancer in never-smoking women married

2501031970

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

to smokers. To extrapolate exposure and consequent risk to other sources of ETS exposure, cotinine levels of never-smokers exposed to spousal ETS are compared with those of never-smokers exposed only to other sources of ETS (background), and it is assumed that excess risks of lung cancer from ETS exposures, using cotinine levels as a surrogate measure, are proportional to current ETS exposure levels. The use of current cotinine data to estimate ETS exposure in nonsmokers seems reasonable because cotinine levels correlate quite well with questionnaire response on ETS exposure. However, the total estimate of population risk is sensitive to uncertainty in making these assumptions and variability in the use of cotinine measures.

This report uses the modeling approach based on direct ETS epidemiologic evidence because the assumptions are fewer and more valid than for the "cigarette-equivalents" approach, and the abundance of human data from actual environmental exposures makes this preferred approach feasible. The total number of lung cancer deaths in U.S. females from all causes is partitioned into components attributable to nontobacco-smoke-related causes (background causes unrelated to active or passive smoking), background ETS (also called nonspousal ETS), spousal ETS, and ever-smoking. Two sets of calculations are made for the U.S. female population of age 35+ in 1985 based on parameter values from national statistics and estimates from the epidemiologic studies on ETS and lung cancer. They differ in the values assumed for two parameters in the formulae for attributable risk: RR_2, the relative risk of lung cancer for never-smokers exposed to spousal smoke, and Z, the ratio of cotinine concentrations in never-smokers exposed to spousal ETS to those exposed to background ETS only. The first analysis uses the pooled estimate of RR_2 from the 11 U.S. studies from Chapter 5, and a subjective value of Z based on the outcomes of independent U.S. cotinine studies (RR_2 = 1.19 and Z = 1.75). The second analysis uses the estimates of RR_2 and Z from the large, high-quality Fontham et al. study (1991), the sole U.S. study that collected cotinine data for its study population (RR_2 = 1.26 with mean Z = 2.0 and with median Z = 2.6).

The estimated lung cancer mortality in never-smoking women from ETS (background and spousal ETS) is 1,500 in the first analysis and 1,630 (1,250) in the second analysis for Z = 2.0 (2.6). When estimates for never-smoking males and former smokers (5+ year quitters) of both sexes are added, the corresponding totals are 3,060 and 3,300 (2,480). All of these figures are based on calculations in which unknown parameter values are replaced with numerical estimates which are subject to uncertainty, and departures in either direction cannot be precluded as unrealistic possibilities for the correct population risks. Nonetheless, because of the large data base utilized and the extensive analysis performed, there is a high degree of confidence in the estimates derived for female never-smokers. The figures for male never-smokers and former

250103197

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

smokers of both sexes are subject to more uncertainty since more assumptions were necessary for extrapolation from the epidemiologic results. The estimates for male never-smokers, in particular, may be on the low side because males are generally exposed to higher levels of background ETS than females. In summary, our analyses support a total of approximately 3,000 as an estimate for the annual U.S. lung cancer deaths in nonsmokers attributable to ETS exposure, with 2,500 to 3,300 comprising a reasonable range of values.

Despite some unavoidable uncertainties, we believe these estimates of ETS-attributable lung cancer mortality to be fairly reliable, if not conservatively low with respect to the male nonsmoker component. First, the weight-of-evidence that ETS is a human lung carcinogen is very strong. Second, the estimates are based on a large amount of data from various studies of human exposures to actual environmental levels of ETS. They do not suffer from a need to extrapolate from an animal species to humans or from high to low exposures, as is nearly always the case in environmental quantitative health risk assessment. Thus, the confidence in these estimates is judged to be medium to high. In summary, the evidence demonstrates that ETS has a very substantial and serious public health impact.

2501031922

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 6-1. Definition and estimates of relative risk of lung cancer for 11 U.S. studies combined for various exposure sources and baselines. Population parameter definitions and estimates used to calculate U.S. population-attributable risk estimates for ETS

DENOMINATOR (Baseline)	NUMERATOR of Relative Risk			
	(All Persons)	Never-Smokers ETS - Exposure		Current and Former Smokers
Source of Exposure	Non-Tobacco - Smoke Sources of Exposure	Background ETS	Background ETS & Spousal ETS	Active Smoking
	[nt]	[nt]+[ETS_B]	[nt]+[ETS_B]+[ETS_S]	[nt]+[ETS]+[ACT]
[nt]	1	RR_{03} = 1.34	RR_{02} = 1.59[b]	RR_{01} = 13.8
[nt]+[ETS_B]	-	-	RR_2 = 1.19[a]	RR_{11} = 10.3
[nt]+[ETS_B]+[ETS_S]	-	-	-	RR_1 = 9.26[c]

a. Pooled Value from 11 U.S. Studies for Never-Smoking Females
b. Basic Adjustment for Background Exposure with Z = 1.75
c. RR_1 = a Weighted Average of 11.94 for Women Active Smokers (63.4%) and 4.69 for Women Former Smokers (36.6%) = 9.26

Definitions and Estimates of Population Parameter Values

N = Total number of women in U.S. (1985) age 35+ = N_1 (ever-smokers) + N_2 (never-smokers) = 25.7 million + 32.3 million = 58 million

P_1 = Prevalence (proportion) of female ever smokers age 35+ = 0.443

P_2 = Proportion of NS women exposed to equivalent spousal ETS (plus background ETS) = 0.6

Z = Ratio of body cotinine levels in (nonsmokers exposed to background ETS plus spousal ETS) to (nonsmokers exposed to background ETS only) = 1.75

T = Total lung cancer deaths in U.S. in 1985 among women aged 35+ = 38,000

DRAFT--DO NOT QUOTE OR CITE

250103197 3
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 6-2. Estimated female lung cancer mortality by attributable sources for United States, 1985, using the pooled relative risk estimate from 11 U.S. studies[1]

			Lung Cancer Mortality[5]				
		(1)	(2)	(3)	(4)	(5)	
Smoking Status[2]	Exposed to Spousal ETS	Number at Risk (x 10^6)	Non-Tobacco-Smoke-Related Causes[3]	Background ETS	Spousal ETS	Ever-Smoking	Total
NS	No	12.92	1,220 (3.2)	410 (1.1)			
NS	Yes	19.38	1,830 (4.8)	620 (1.6)	470 (1.2)		
ES		25.69	2,420 (6.4)			31,030[4] (81.7)	
Total		58.00	5,470 (14.4)	1,030 (2.7)	470 (1.2)	31,030 (81.7)	38,000

[1]Percent of grand total (38,000) in parentheses.
[2]NS: never-smokers; ES: ever-smokers.
[3]Background sources in the absence of tobacco smoke (i.e., in a zero-ETS environment).
[4]This figure attributes all lung cancer in ever-smokers above the background non-tobacco-smoke-related rate to ever-smoking.

DRAFT--DO NOT QUOTE OR CITE

5/15/92 2501031974

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

DRAFT--DO NOT QUOTE OR CITE

Table 6-2. (continued)

[5]The nonblank entries in the table are the product of an individual's attributable risk of lung cancer from nontobacco-smoke-related causes (expression 6-9 (38,000/58,000,000)), the number at risk in column (1), and the following column-specific multiples:

Col. (2)	1
Col. (3)	$RR_{03} - 1$
Col. (4)	$RR_{02} - RR_{03}$
Col. (5)	$RR_{01} - 1$

250103197S
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 6-3. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using 11 U.S. studies (never-smokers and former smokers who have quit 5+ years)[1]

				Lung Cancer Mortality			
			(1)	(2)	(3)	(4)	
Smoking Status[2]	Sex	Exposed to Spousal ETS	Number at Risk (x 10^6)	Background ETS	Spousal ETS	Total ETS	Total ETS by Sex and Smoking Status
NS	F	No	12.92	410		410	1,500 (NS,F)
NS	F	Yes	19.38	620	470	1,090	
NS	M	No	9.93	320		320	500 (NS,M)
NS	M	Yes	3.13	100	80	180	
FS	F	No	2.0	60		60	430 (FS,F)
FS	F	Yes	6.7	210	160	370	

DRAFT--DO NOT QUOTE OR CITE

250103976

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 6-3. (continued)

FS	M	No	8.8	280		280	630 (FS,M)
FS	M	Yes	6.2	200	150	350	
Total			69.07	2,200 (71.9)	860 (28.1)	3,060	3,060

[1]Percent of total ETS-attributable lung cancer deaths (3,060) in parentheses.
[2]NS: never-smokers; FS: former smokers who have quit 5+ years ago.

DRAFT--DO NOT QUOTE OR CITE

250103197?
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 6-4. Female lung cancer mortality estimates by attributable sources for United States, 1985, using both the relative risk estimates and Z-values from the Fontham et al. study[1]

Smoking Status[2]	Exposed to Spousal ETS	(1) Number at Risk (x 10^6)	Lung Cancer Mortality[5] (2) Non-Tobacco-Smoke-Related Causes[3]	(3) Background ETS	(4) Spousal ETS	(5) Ever-Smoking	Total
NS	No	12.92	1,160 (3.1) *1,320 (3.5)*	410 (1.1) *260 (0.7)*			
NS	Yes	19.38	1,750 (4.6) *1,970 (5.2)*	610 (1.6) *380 (1.0)*	610 (1.6) *610 (1.6)*		
ES		25.69	2,310 (6.1) *2,620 (6.9)*			31,140[4] (82.0) *30,840[4] (81.2)*	
Total		58.00	5,220 (13.7) *5,910 (15.6)*	1,020 (2.7) *640 (1.7)*	610 (1.6) *610 (1.6)*	31,140 (82.0) *30,840 (82.0)*	38,000

[1]Percent of grand total (38,000) in parentheses. Calculations using Z=2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z=2.6 (ratio of median cotinine levels) are shown in italics.
[2]NS: never-smokers; ES: ever-smokers.

05/15/92
DRAFT--DO NOT QUOTE OR CITE
250103978
Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

DRAFT--DO NOT QUOTE OR CITE

Table 6-4. (continued)

[3]Baseline lung cancer mortality in the absence of tobacco smoke (i.e. in a zero-ETS environment).
[4]This figure attributes all lung cancer in ever-smokers above the non-tobacco-smoke-related rate to active-smoking.
[5]See Table 6-2 for formulae for table entries.

05/15/92
2501031979

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 6-5. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using the Fontham et al. study (never-smokers and former smokers who have quit 5+ years)[1,2]

Smoking Status[3]	Sex	Exposed to Spousal ETS	(1) Number at Risk (x 10^6)	Lung Cancer Mortality (2) Background ETS	(3) Spousal ETS	(4) Total ETS	Total ETS by Sex and Smoking Status
NS	F	No	12.92	410 *260*		410 *260*	1,630 *1,250* (NS,F)
NS	F	Yes	19.38	610 *380*	610 *610*	1,220 *990*	
NS	M	No	9.93	310 *200*		310 *196*	510 *360* (NS,M)
NS	M	Yes	3.13	100 *60*	100 *100*	200 *160*	
FS	F	No	2.0	60 *40*		60 *40*	480 *380* (FS,F)
FS	F	Yes	6.7	210 *130*	210 *210*	420 *340*	

DRAFT--DO NOT QUOTE OR CITE

250103198O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 6-5. (continued)

Smoking Status[3]	Sex	Exposed to Spousal ETS	(1) Number at Risk ($\times 10^6$)	Lung Cancer Mortality (2) Background ETS	(3) Spousal ETS	(4) Total ETS	Total ETS by Sex and Smoking Status
FS	M	No	8.8	280 *170*		280 *170*	680 *490* (FS,M)
FS	M	Yes	6.2	200 *120*	200 *200*	400 *320*	
Total			69.07	2,180 (66.1) *1,360 (54.9)*	1,120 (33.9) *1,120 (45.1)*	3,300 *2,480*	3,300 *2,480*

[1]Calculations using Z=2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z=2.6 (ratio of median cotinine levels) are shown in italics.
[2]Percent of total ETS-attributable lung cancer deaths (3,300; *2,480*) in parentheses.
[3]NS: never-smokers; FS: former smokers who have quit 5+ years ago.

DRAFT--DO NOT QUOTE OR CITE

250103198I
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 6-6. Effect of single parameter changes on lung cancer mortality due to ETS in never-smokers and former smokers who have quit 5+ years

Parameter Change		LCM Due to ETS Background[1]	Spousal[2]	Total	Percent Change[3]
None[4]		**2,210**	**850**	**3,060**	**0**
Z =	**1.50**	3,310	850	4,160	+36
	1.75	**2,210**	**850**	**3,060**	**0**
	2.00	1,660	850	2,510	-18
	2.25	1,320	850	2,170	-29
	2.50	1,100	850	1,950	-36
	2.75	950	850	1,800	-41
	3.00	830	850	1,680	-45
RR_2 =	1.04	510	190	700	-77
	1.05	630	240	870	-72
	1.10	1,220	470	1,690	-45
	1.15	1,780	690	2,470	-19
	1.19	**2,210**	**850**	**3,060**	**0**
	1.20	2,310	890	3,200	+5
	1.25	2,820	1,080	3,900	+27
	1.30	3,290	1,270	4,560	+49
	1.35	3,750	1,440	5,190	+70
RR_1 =	8.00	2,510	970	3,480	+14
	8.50	2,380	920	3,300	+8
	9.00	2,260	870	3,130	+3
	9.26	**2,210**	**850**	**3,060**	**0**
	9.50	2,160	830	2,990	-2
	10.00	2,060	800	2,860	-7
	10.50	2,020	780	2,800	-9
	11.00	1,890	730	2,620	-14

[1]69,100,000 at risk.
[2]35,400,000 at risk.
[3]Percent change from total shown in boldface. (The outcome from Tables 6-2 and 6-3, using the 11 U.S. studies).
[4]Z=1.75, RR_2=1.19, RR_1=9.26.

250103982

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

7. PASSIVE SMOKING AND RESPIRATORY DISORDERS OTHER THAN CANCER

7.1. INTRODUCTION

In 1984, a report of the Surgeon General identified cigarette smoking as the major cause of chronic obstructive lung disease in the United States (U.S. DHHS, 1984). The same report stated that there is conclusive evidence showing that smokers are at increased risk of developing respiratory symptoms such as chronic cough, chronic phlegm production, and wheezing (U.S. DHHS, 1984). More recently, longitudinal studies have demonstrated accelerated decline in lung function in smoking adults (Camilli et al., 1987). In children and adolescents who have recently taken up smoking, several cross-sectional studies have found statistically significant increases in the prevalence of respiratory symptoms (cough, phlegm production, and dyspnea [i.e., shortness of breath]) (Seely et al., 1971; Bewley et al., 1973). Longitudinal studies have also demonstrated that, among young teenagers, functional impairment attributable to smoking may be found after as little as 1 year of smoking 10 or more cigarettes per week (Woolcock et al., 1984).

From a pathophysiologic point of view, smoking is associated with significant structural changes in both the airways and the pulmonary parenchyma (U.S. DHHS, 1984). These changes include hypertrophy and hyperplasia of the upper airway mucus glands, leading to an increase in mucus production, with an accompanying increased prevalence of cough and phlegm. Chronic inflammation of the smaller airways leads to bronchial obstruction. However, airway narrowing may also be due to the destruction of the alveolar walls and the consequent decrease in lung elasticity and development of centrilobular emphysema (Bellofiore et al., 1989). Smoking may also increase mucosal permeability to allergens. This may result in increased total and specific IgE levels (Zetterstrom et al., 1981) and increased blood eosinophil counts (Halonen et al., 1982).

The ascertained consequences of active smoking on respiratory health, and the fact that significant effects have been observed at relatively low-dose exposures, leads to an examination for similar effects with environmental tobacco smoke (ETS). Unlike active smoking, involuntary exposure to ETS (or "passive smoking") affects individuals of all ages, and particularly infants and children. An extensive analysis of respiratory effects of ETS in children suggests that the lung of the young child may be particularly susceptible to environmental insults (NRC, 1986). Exposures in early periods of life during which the lung is undergoing significant growth and remodeling may alter the pattern of lung development and increase the risk for both acute and chronic respiratory illnesses.

Acute respiratory illnesses are one of the leading causes of morbidity and mortality during infancy and childhood. One-third of all infants have at least one lower respiratory tract illness

250103 1983

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

(bronchitis, bronchiolitis, croup, or pneumonia) during the first year of life (Wright et al., 1989), whereas approximately one-fourth have these same illnesses during the second and third years of life (Gwinn et al., 1991). The high incidence of these potentially severe illnesses has an important consequence from a public health viewpoint: Even small increases in risk due to passive exposure to ETS would considerably increase the absolute number of cases in the first 3 years of life (see Chapter 8). In addition, several studies have shown that lower respiratory tract illnesses occurring early in life are associated with a significantly higher prevalence of asthma and other chronic respiratory diseases and with lower levels of respiratory function later in life (reviewed extensively by Samet and collaborators [1983]).

This chapter reviews and analyzes epidemiologic studies of noncancer respiratory system effects of passive smoking, starting with possible biological mechanisms (Section 7.2). The evidence indicating a relationship between exposure to ETS during childhood and acute respiratory illnesses (7.3), middle ear disease (7.4), chronic respiratory symptoms (7.5), asthma (7.6), sudden infant death syndrome (7.7), and lung function impairment (7.8) is evaluated. Passive smoking as a risk factor for noncancer respiratory illnesses and lower lung function in adults is also analyzed (7.9). Finally, a health hazard assessment and population impact is presented in the next chapter.

7.2. BIOLOGICAL MECHANISMS

7.2.1. Plausibility

It is plausible that passive smoking may produce effects similar to those known to be elicited by active smoking. However, several differences both between active and passive forms of exposure and among the individuals exposed to them need to be considered.

The concentration of smoke components inhaled by subjects exposed to ETS is small compared with that from active smoking. Therefore, effect will be highly dependent on the nature of the dose-response curve (NRC, 1986). It is likely that there is a distribution of susceptibility to the effects of ETS that may depend on, among other factors, age, gender, genetic predisposition, previous respiratory history, and concomitant exposure to other risk factors for the particular outcome being studied. The ability to ascertain responses to very low concentrations also depends on the reliability and sensitivity of the instruments utilized.

Breathing patterns for the inhalation of mainstream smoke (MS) and ETS differ considerably; active smokers inhale intensely and intermittently, and usually hold their breath for some time at the end of inspiration. This increases the amount of smoke components that are deposited and absorbed (U.S. DHHS, 1986). Passive smokers inhale with tidal breaths and

2501031984

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

continuously. Therefore, patterns of particle deposition and gas diffusion and absorption differ considerably for these two types of inhalation.

There are also important differences in the physicochemical properties of ETS and MS (see Chapter 3). These have been extensively reviewed earlier by the National Research Council (NRC, 1986) and the Surgeon General (U.S. DHHS, 1986). ETS is a combination of exhaled MS, sidestream smoke (that is, the aerosol that is emitted from the burning cone between puffs), smoke emitted from the burning side of the cigarette during puffs, and gases that diffuse through the cigarette paper into the environment. This mixture may be modified by reactions that occur in the air before involuntary inhalation. This "aging" process includes volatilization of nicotine, which is present in the particulate phase in MS but is almost exclusively a component of the vapor phase of ETS. Aging of ETS also entails a decrease in the mean diameter of its particles from 0.32 μm to 0.1-0.14 μm, compared to a mean particle diameter for MS of 0.4 μm (NRC, 1986).

Individual and socioeconomic susceptibility may be important determinants of possible effects of ETS on respiratory health. A self-selection process almost certainly occurs among subjects who experiment with cigarettes, whereby those more susceptible to the irritant and/or sensitizing effects of tobacco smoke either never start or quit smoking (the so-called "healthy smoker" effect). Infants, children, and nonsmoking adults may thus include a disproportionate number of susceptible subjects when compared to smoking adults. In addition, recent studies have clearly shown that, as incidence and prevalence of cigarette smoking has decreased, the socioeconomic characteristics of smokers have also changed. Among smokers, the proportion of subjects of lower educational level has increased in the last 20 years (Pierce et al., 1989). The female-to-male ratio has also increased (Fiore et al., 1989), and this is particularly true for young, poor women, in whom incidence and prevalence of smoking has increased (Williamson et al., 1989). It is thus possible that exposure to ETS may be most prevalent today among precisely those infants and children that are known to be at a high risk of developing respiratory illnesses early in life.

7.2.2. Effects of Exposure In Utero and During the First Months of Life

A factor that may significantly modify the effect of passive smoking (particularly in children) is exposure to tobacco smoke components by the fetus during pregnancy. This type of exposure differs considerably from passive smoking; in fact, the fetus (including its lungs) is exposed to components of tobacco smoke that are absorbed by the mother and that cross the placental barrier, whereas passive smoking directly affects the bronchial mucosa and the alveolus. It is difficult to distinguish between the possible effects of smoking during pregnancy and those

2501031985

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

of ETS exposure after birth. Some women may quit smoking during pregnancy, only to resume after pregnancy is over. Most mothers who smoke during pregnancy continue smoking after the birth of their child (Wright et al., 1991), and among those who stop smoking after birth, the influence on that decision of events occurring shortly after birth (such as respiratory illnesses in their child) cannot be excluded. Recall bias may also influence the results of retrospective studies claiming differential effects on lung function of prenatal and postnatal maternal smoking habits (Yarnell and St. Leger, 1979).

To attempt to circumvent these problems, researchers have studied infant lung function shortly after birth (the youngest group of infants reported was 2 weeks old [Neddenriep et al., 1990]), with the implication that subsequent changes encountered could be attributed mainly to ETS exposures. However, the possibility that even brief exposures to ETS may affect the lungs at a highly susceptible age may not be discarded. Maternal smoking during pregnancy needs to be considered, therefore, as a potential modifier of the effect of passive smoking on respiratory health, particularly in children.

Exposure to compounds present in tobacco smoke may affect the fetal and neonatal lung and alter lung structure much like these same compounds do in smoking adults. Neddenriep and coworkers (1990) studied 31 newborns and reported that those whose mothers smoked during pregnancy had significant increases in specific lung compliance (i.e., lung compliance/lung volume) at 2 weeks of age when compared with infants of nonsmoking mothers. The authors concluded that exposure to tobacco products detrimentally affects the elastic properties of the fetal lung. Although these effects could also be attributed to postnatal exposure to ETS, it is unlikely that such a brief period of postnatal exposure would be responsible for these changes affecting the lung parenchyma (U.S. DHHS, 1986).

There is evidence for similar effects in animal models of prenatal lung development. Collins and associates (1985) exposed pregnant rats to MS during day 5 to day 20 of gestation. They found that pups of exposed rats showed reduced lung volume, reduced number of lung saccules, and reduced length of elastin fibers in the lung interstitium. This apparently resulted in a decrease in lung elasticity: For the same inflation pressure, pups of exposed mothers had significantly higher weight-corrected lung volumes than did pups of unexposed mothers. Vidic and coworkers (1989) exposed female rats for 6 months (including mating and gestation) to MS. They found that lungs of their 15-day-old pups had less parenchymal tissue, less extracellular matrix, less collagen, and less elastin than found in lungs of control animals. This may explain the increased lung compliance observed by Collins et al. (1985) in pups exposed to tobacco smoke products in utero.

250103198

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Hanrahan and coworkers (1990) reported that infants born to smoking mothers had significantly reduced levels of forced expiratory flows. They studied 80 mother/child pairs and found significant correlations between the cotinine/creatinine ratio in urine specimens obtained during pregnancy in the mother and maximal expiratory flows and tidal volumes at a postconceptional age of 50 weeks or less in their children. They concluded that exposure due to prenatal smoking diminishes infant pulmonary function at birth and, by inference, airway size. These authors also measured maximal flows during tidal breathing in their subjects. At rather low lung volumes, such as those present during tidal breathing, airway size and maximal flows are both a function of lung elasticity. These results may thus be due to both a specific alteration of the infant's airways and an increased lung compliance in infants whose lungs are small relative to the infant's length.

It has also been suggested that the increased IgE levels observed in adult smokers may also be present among fetuses whose mothers smoke during pregnancy. Magnusson (1986) reported that cord serum levels of IgE and IgD were significantly higher for neonates whose mother smoked during pregnancy, particularly if the neonates had no parental history of allergic disorders. Cord serum levels of IgD (but not of IgE) were increased for neonates whose fathers smoked, and this effect was independent of maternal smoking. A more recent study on a larger sample (over 1,000 neonates) failed to find any significant difference in cord serum IgE levels between infants (N = 193) of mothers who smoked during pregnancy and those (N = 881) of mothers who did not (Halonen et al., 1991).

It has also been recently reported that the pulmonary neuroendocrine system may be altered in infants whose mothers smoke during pregnancy. The pulmonary neuroendocrine system, located in the tracheobronchial tree, consists of specialized cells (isolated or in clusters called "neuroepithelial bodies") that are closely related to nerves. In humans, these cells increase in number significantly during intrauterine development, reach a maximum around birth, and then rapidly decline during the first 2 years of life. Their function is not well understood, but the presence of potent growth factors and bronchoconstrictive substances in their granules suggests that they play an important role in growth regulation and airway tone control during this period of lung development (Stahlman and Gray, 1984). Chen and coworkers (1987) reported that maternal smoking during pregnancy increases the size of infant lung neuroepithelial bodies and decreases the amount of core granules present in them. Wang and coworkers (1984) had previously reported that mother mice receiving tap water with nicotine during pregnancy and during lactation had offspring with increased numbers of neuroepithelial bodies at 5 days of age when compared to baby mice whose mothers were not exposed. Baby mice exposed to nicotine

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

only during pregnancy had neuroepithelial bodies of intermediate size with respect to these two groups, whereas those exposed only during lactation had neuroepithelial bodies of normal size. By age 30 days, only baby mice exposed to nicotine during both pregnancy and lactation had neuroepithelial bodies that were larger than those of control animals.

Activation of the pulmonary neuroendocrine system is not limited to ETS exposure; it is activated by active smoking as well. Aguayo and collaborators (1989) reported that bronchoalveolar lavage fluids obtained from healthy smokers have increased levels of bombesin-like peptides, which are a normal component and a secretion product of human lung neuroendocrine cells (Cutz et al., 1981).

In summary, effects of maternal smoking during pregnancy on the fetus are difficult to distinguish from those elicited by early postnatal exposure to ETS. Animal studies suggest that postnatal exposure to tobacco products enhances the effects of in utero exposure to these same products.

7.2.3. Long-Term Significance of Early Effects on Airway Function

By altering the structural and functional properties of the lung, prenatal exposure to tobacco smoke products and early postnatal exposure to ETS increase the likelihood of more severe complications during viral respiratory infections early in life. Martinez and collaborators (1988a) measured lung function before 6 months of age and before any lower respiratory illness in 124 infants. They found that infants with the lowest levels for various indices of airway size were 3-9 times more likely to develop wheezing respiratory illnesses during the first year of life than the rest of the population. The same authors (Martinez, 1991a) subsequently showed that, in these same infants with lower initial levels of lung function, recurrent wheezing illnesses were also more likely to occur during the first 3 years of life. A similar study performed in Australia (Young et al., 1990) confirmed that infants who present episodes of cough and wheeze during the first 6 months of life have lower maximal expiratory flows before any such illnesses develop.

The increased likelihood of pulmonary complications during viral respiratory infections in infants of smoking parents has important long-term consequences for the affected individual. There is considerable evidence suggesting that subjects with chronic obstructive lung diseases have a history of childhood respiratory illnesses more often than subjects without such diseases (reviewed by Samet and coworkers [1983]). Burrows and collaborators (1988) found that active smokers without asthma (N = 41) who had a history of respiratory troubles before age 16 years showed significantly steeper declines in FEV_1 (as a percentage of predicted) after the age of 40 than did nonasthmatic smokers without such a history (N = 396). Although these results may have

25010319 88

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

been influenced by recall bias, they suggest that lower respiratory tract illnesses during a period of rapid lung development may damage the lung and increase the susceptibility to potentially harmful environmental stimuli.

There is no information available on the degree of reversibility of changes induced by exposure to ETS during early life. Longitudinal studies of lung function in older children have shown, however, that diminished levels of lung function are found in children of smoking parents at least until the adolescent years (see below).

7.2.4. Exposure to ETS and Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness consists of an enhanced sensitivity of the airways to pharmacologic or physical stimuli that normally produce no changes or only small decreases in lung function in normal individuals. Subjects with bronchial hyperresponsiveness have significant drops in airway conductance and maximal expiratory flows after inhalation of stimuli such as cold air, hypertonic saline, nebulized distilled water, methacholine, or histamine. Bronchial hyperresponsiveness is regarded as characteristic of asthma (O'Connor et al., 1989) and may precede the development of this disease in children (Hopp et al., 1990). It has also been considered as a predisposing factor for chronic airflow limitation in adult life (O'Connor et al., 1989).

Recent studies of large population samples have shown that active smokers have increased prevalence of bronchial hyperresponsiveness (Woolcock et al., 1987; Sparrow et al., 1987; Burney et al., 1987) when compared with nonsmokers. This relationship seems to be independent of other possible determinants of bronchial hyperresponsiveness (O'Connor et al., 1989). However, one large study of almost 2,000 subjects from a general population sample failed to find a significant relationship between smoking and prevalence of bronchial hyperresponsiveness (Rijcken et al., 1987). The subjects involved in the latter study were younger and were therefore exposed to a smaller average cumulative pack-years of smoking than were the subjects of studies in which a positive relationship was found. This suggests that the relationship may be evident only among individuals with a high cumulative exposure.

Epidemiologic studies have demonstrated that exposure to ETS is associated with an increased prevalence of bronchial hyperresponsiveness in children. Murray and Morrison (1986), in a cross-sectional study, reported that asthmatic children of smoking mothers were four times more likely to show increased responsiveness to histamine than were asthmatic children of nonsmoking mothers. O'Connor and coworkers (1987), in a study of a general population sample, found a significant association between maternal smoking and bronchial hyperresponsiveness (as

250103198

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

assessed with eucapnic hyperpnea with subfreezing air) among asthmatic children, but not among nonasthmatic children (Weiss et al., 1985). Martinez and coworkers (1988b) reported a fourfold increase in bronchial responsiveness to carbachol among male children of smoking parents when compared to male children of parents who were both nonsmokers. A smaller (and statistically not significant) increase in bronchial responsiveness was reported in girls. These authors also found that the effect of parental smoking was stronger in asthmatic children, and results were still significant after controlling for this factor in a multivariable analysis. Because only a small proportion of mothers in this population smoked during pregnancy, the effect was considered to be associated mainly with exposure to ETS in these children. Lebowitz and Quackenboss (1990) showed that odds of having bronchial reactivity (as assessed by the diurnal variability in maximal expiratory flow rate) were 3.6 times as high among 18 children aged < 15 years who lived with smokers of > 20 cigarettes per day than among 62 children of the same age who lived with nonsmokers (95% CI = 1.2-10.6). Children living with smokers of 1 to 20 cigarettes per day had a prevalence of bronchial reactivity that was similar to that of children living with nonsmokers.

There is, therefore, evidence indicating that parental smoking enhances bronchial responsiveness in their children. The mechanism for this effect and the possible role of atopy in it (see below) are unknown. The doses required to enhance bronchial responsiveness in children exposed to ETS are apparently much lower than those required to elicit similar effects among adult active smokers. A process of self-selection, by which adults who are more sensitive to the effects of tobacco smoke do not start smoking or quit smoking earlier, may explain this finding. Variations in bronchial responsiveness with age may also be involved (Hopp et al., 1985).

7.2.5. ETS Exposure and Atopy

Atopy has been defined epidemiologically as the presence of immediate hypersensitivity to at least one potential allergen administered by skin prick test. Atopy is an immediate form of hypersensitivity to antigens (called allergens) that is mediated by IgE immunoglobulin. Allergy (as indicated by positive skin test reactivity to allergens, high levels of circulating IgE, or both) is known to be present in almost all cases of childhood asthma. Recent epidemiologic studies have indicated that an IgE-mediated reaction may be necessary for the occurrence of almost all cases of asthma at any age (Burrows et al., 1989).

Although genetic factors appear to play a major role in the regulation of IgE production (Meyers et al., 1987; Hanson et al., 1991), several reports have indicated that active smoking significantly increases total serum IgE concentrations and may thus influence the occurrence of allergy (Gerrard et al., 1980; Burrows et al., 1981; Zetterstrom et al., 1981; Taylor et al., 1985).

250103199O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Active smokers have also been found to have higher eosinophil counts and increased prevalence of eosinophilia when compared to nonsmokers (Kauffmann et al., 1986; Halonen et al., 1982; Taylor et al., 1985). The physical and chemical similarities between MS and ETS have prompted the investigation of a possible role of passive smoking in allergic sensitization in children.

Weiss and collaborators (1985) first reported a 2.2-fold increased risk of being atopic in children of smoking mothers. Martinez and coworkers (1988b) confirmed that children of smoking parents were significantly more likely to be atopic than were children of nonsmoking parents, and reported that this association was stronger for male children. They also found a rough dose-response relationship between the number of cigarettes smoked by parents and the intensity of the skin reactions to a battery of allergens. Ronchetti and collaborators (1990) extended these findings in the same population sample of Martinez and coworkers. They found that total serum IgE levels and eosinophil counts were significantly increased in children of smoking parents, and the effect was related to both maternal and paternal smoking.

It is relevant to note that, due to the so-called "healthy smoker effect," children of smokers should be genetically less sensitive than children of nonsmokers, because the latter are likely to include a disproportionate number of allergic subjects who are very sensitive to the irritant effects of smoke. As a consequence, the atopy-inducing effects of ETS may be substantially underestimated.

In summary, there is convincing evidence that both maternal smoking during pregnancy and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization. These changes elicited by exposure to tobacco products may predispose children to lower respiratory tract illnesses early in life, and to asthma, lower levels of lung function, and chronic airflow limitation later in life. Most of these same effects have been described for active smoking in adults. These smoke-induced changes are, therefore, known biological mechanisms for the increased prevalence of respiratory diseases associated with ETS exposure described later in this chapter.

Exposure to tobacco smoke products during pregnancy and to ETS soon after birth may be the most important preventable cause of early lung and airway damage leading to both lower respiratory illness in early childhood and chronic airflow limitation later in life.

7.3. EFFECT OF PASSIVE SMOKING ON ACUTE RESPIRATORY ILLNESSES IN CHILDREN

A review of the literature that examined the effects of exposure to ETS on the acute respiratory illness experiences of children was contained in the Surgeon General's report on the

250103199

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

health consequences of involuntary smoking (U.S. DHHS, 1986) and in the report on environmental tobacco smoke by the NRC (1986). Table 7-1 shows the studies referenced in these two reports.

The Surgeon General's report concluded that "the results of these studies show excess acute respiratory illness in children of parents who smoke, particularly in children under 2 years of age" (page 44) and that "this pattern is evident in studies conducted with different methodologies and in different locales" (page 44). It estimated that the increased risk of hospitalization for severe bronchitis or pneumonia ranged from 20% to 40% during the first year of life. The report stated that "young children appear to be a more susceptible population for the adverse effects of involuntary smoking than older children and adults" (page 44). Finally, the report suggested that "acute respiratory illnesses during childhood may have long-term effects on lung growth and development, and might increase the susceptibility to the effects of active smoking and to the development of chronic lung disease" (page 44).

The 1986 NRC report observed that "all the studies that have examined the incidence of respiratory illnesses in children under the age of 1 year have shown a positive association between such illnesses and exposure to ETS. The association is very unlikely to have arisen by chance" (page 208). It pointed out that "some of the studies have examined the possibility that the association is indirect by allowing for confounding factors . . . and have concluded that such factors do not explain the results. This argues, therefore, in favor of a causal explanation" (page 208). The report concluded that "bronchitis, pneumonia, and other lower-respiratory-tract illnesses occur up to twice as often during the first year of life in children who have one or more parents who smoke than in children of non-smokers" (page 217).

7.3.1. Recent Studies on Acute Lower Respiratory Illnesses

Several recent studies not referenced in the Surgeon General's Report or in the NRC report have addressed the relationship between parental smoking and acute lower respiratory illnesses in children (see Table 7-2).

Chen and coworkers (1986) studied 1,058 infants out of 1,163 infants born in a given period in two neighborhoods in Shanghai, People's Republic of China. Information on hospital admissions from birth to 18 months, smoking habits of household members, parental education, and social and living conditions was obtained by use of a self-administered questionnaire completed by the parents when the child reached 18 months of age. Hospital admissions were divided into those due to respiratory illness and those from all other conditions. None of the mothers in the study smoked. There was no statistically significant association between exposure

250103199 2

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

to ETS and admission to the hospital for any condition other than respiratory illnesses. Compared to nonsmoking households, the risk of being admitted to a hospital for respiratory illnesses was 17% higher when 1 to 9 cigarettes were smoked daily by household members (95% C.I. = 0.6-2.3), and was 89% higher when > 9 were smoked daily by household members (95% C.I. = 1.1-3.4). The authors controlled for the effects of crowding, chronic respiratory illness in the family, father's education, type of feeding, and birthweight.

Chen and coworkers (1988) subsequently studied 2,227 out of 2,315 children born in the last quarter of 1983 in Chang-Ning District, Shanghai, People's Republic of China. There were no smoking mothers in this population. The authors reported a significant linear relationship of total daily cigarette consumption by family members with incidence density of hospitalization for respiratory illness and with cumulative incidence of bronchitis and pneumonia in the first 18 months of life. The relationship was stronger for the 1- to 6-month period than for the 7- to 18-month period: When compared to households whose members did not smoke at home, the risk of being hospitalized for respiratory illness during the 1- to 6-month interval was three times as high (95% C.I. = 1.6-5.7) in households whose members smoked > 9 cigarettes at home, whereas comparison of the same two types of household showed that the risk of being hospitalized for respiratory illness during the 7- to 18-month interval was only 1.8 times as high (95% C.I. = 1.0-3.2) in the smoking household. The relationship was also stronger among low-birthweight infants. Results were independent of sex, birthweight, feeding practices, nursery care, paternal education, family history of chronic respiratory diseases, and use of coal for cooking.

In a different publication based on the same data from the 1988 study, Chen (1989) reported that the effects of passive smoking were stronger in artificially fed infants than in breast-fed infants. When compared to breast-fed infants of nonsmoking families, the risk of being hospitalized for respiratory illness in the first 18 months of life was 1.6 times as high for breast-fed infants of smoking families (> 19 cig./day), whereas the same risk was 3.4 times as high among non-breast-fed infants of smoking families.

The studies by Chen and coworkers (1986, 1988, 1989) were retrospective in nature and thus not immune to possible biases generated by the fact that the occurrence of the outcome event may enhance reporting or recall of the conditions considered as risk factors. However, conclusions are strengthened by the finding that admissions for *non*respiratory illnesses were unrelated to passive smoking in the study in which the relationship was assessed (Chen, 1986) and by the fact that the finding remained significant after adjusting for known confounders.

250103193

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Breese-Hall and coworkers (1984) studied 29 infants hospitalized with confirmed respiratory syncytial virus (RSV) bronchiolitis before age 2, 58 controls hospitalized for acute nonrespiratory conditions, and 58 controls hospitalized for acute lower respiratory illnesses from causes other than RSV. Cases and controls were matched for age, sex, race, month of admission, and form of payment for hospitalization. Information on smoking habits in the family was obtained at the time of each patient's admission. Cases were 4.8 times as likely as controls (95% C.I. = 1.8-13.0) to have one or more household members who smoked 5 or more cigarettes per day. However, there was no significant difference in the prevalence of cigarette smoking in the households of subjects with respiratory illnesses caused by RSV and those not caused by RSV. This was attributable to the fact that the controls with respiratory illnesses not caused by RSV were also much more likely to live with smokers of 5 or more cigarettes per day than were controls with nonrespiratory illnesses (OR = 2.7, 95% C.I. = 1.3-5.7). Little information is given about enrollment and refusals; thus, it is not possible to know if selection bias may have influenced the results. Also, other possible confounders such as socioeconomic level were not taken into account when matching cases to controls or when data were analyzed.

McConnochie and Roghmann (1986a) compared 53 infants drawn from the patient population of a group practice in Rochester, New York, who had physician-diagnosed bronchiolitis before age 2 years, with 106 controls from the same practice who did not have lower respiratory illnesses during the first 2 years of life and who were matched with cases for sex and age. Parental interviews were conducted when the child had a mean age of 8.4 years. Parents were asked about family history of respiratory conditions and allergy, socioeconomic status, passive smoking, home cooking fuel, home heating methods, and household pets. Passive smoking was defined as current and former smoking of "at least 20 packs of cigarettes or 12 oz of tobacco while living in the home with the subject." Current and former smoking was scored equally, based on the assumption that the report of either reflected passive smoking in the first 2 years of life. Frequency of paternal smoking was not increased among children who had bronchiolitis. Cases were 2.4 times (95% C.I. = 1.2-4.8) as likely to have smoking mothers as were controls. The association was stronger in families with older siblings (OR = 8.9); however, a multiplicative test for this interaction did not reach statistical significance. The authors studied 63% of eligible cases and 34% of eligible controls. Although the reasons for exclusion from both groups are detailed, selection bias cannot be completely excluded, and the authors give no information about maternal smoking habits among excluded subjects. Also, overreporting of smoking by parents who were aware of their child's history of bronchiolitis may have introduced biases due to differential

250103199H

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

misclassification. However, the results were consistent across groups classified according to family history of asthma or allergy, social status, presence of older siblings, and crowding.

Ogston and coworkers (1987) conducted a prospective study of 1,565 infants of primigravidae enrolled antenatally in the Tayside Morbidity and Mortality Study in New Zealand. Information on the father's smoking habits and on the mother's smoking habits during pregnancy was obtained at the first antenatal interview and from a postnatal questionnaire. A summary record was completed when the child was 1 year of age and included a report of the child's respiratory illnesses (defined as "infections of the upper or lower respiratory tract") during the first year of life derived from observations made by health visitors during scheduled visits to see the child. The authors used a multiple logistic regression to control for the possible effects of maternal age, feeding practices, heating type, and father's social class on the relationship between parental smoking and child health. Of the 588 children of nonsmokers in this sample, 146 (24.8%) had respiratory illnesses during the first year of life. Paternal smoking was associated with a 43% increase (95% C.I. = 4.7%-96.1%) in the risk of having respiratory illnesses in the first year of life, and this was independent of maternal smoking. The risk of having a respiratory illness was 82% higher (95% C.I. = 25.6%-264.4%) in infants of smoking mothers than in infants of nonsmoking parents. Smoking by both parents did not increase the risk of having respiratory illnesses beyond the level observed in infants with smoking mothers and nonsmoking fathers. It is difficult to compare this study with other reports on the same issue because the authors could not distinguish between upper and lower respiratory tract illnesses.

Anderson and coworkers (1988) performed a case-control study of 102 infants and young children hospitalized in Atlanta, Georgia, for lower respiratory tract illnesses before age 2 and 199 age- and sex-matched controls. The unadjusted relative odds of having any family member smoking cigarettes were 2.0 times as high ($p < 0.05$) among cases as among controls (confidence interval was not calculable from the reported data). The effect disappeared, however, after controlling for other factors (prematurity, history of allergy in the child, feeding practices, number of persons sleeping in the same room with the child, immunization of the child in the last month) in a multivariable logistic regression analysis. No information is provided in this report about maternal and paternal smoking separately, and the number of cigarettes smoked at home by each family member was not recorded either. Also, almost 30% of all target cases declined participation in the study, and no information was available on smoking habits in the families of these children. No information is given about number of refusals among controls.

Woodward and collaborators (1990) obtained information about the history of acute respiratory illnesses in the previous 12 months on 2,125 children aged 18 months to 3 years whose

250103199

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

parents answered a questionnaire mailed to 4,985 eligible families in Adelaide, Australia. A "respiratory score" was calculated from responses to questions regarding 13 different upper and lower respiratory illnesses. A total of 1,218 parents (57%) gave further consent for a home interview. From this total, parents of 258 cases (children whose respiratory score fell in the top 20% of scores) and 231 "controls" (children whose scores were within the bottom 20% of scores) were interviewed at home. When compared to controls, cases were twice as likely to have a mother who smoked during the first year of life (95% C.I. = 1.3-3.4). This effect was independent of parental history of respiratory illnesses, other smokers in the home, use of group child care, parental occupation, and level of maternal stress and social support. The authors found no differences in the way smokers and nonsmokers perceived or managed acute respiratory illnesses in their children. Based on this finding, they ruled out that such differences could explain their findings. They also reported that feeding practices strongly modified the effect of maternal smoking; among breast-fed infants, cases were 1.8 times as likely to have smoking mothers as were controls (95% C.I. = 1.2-2.8), whereas among non-breast-fed infants, cases were 11.5 times as likely to have smoking mothers as were controls (95% C.I. = 3.4-38.5).

Wright and collaborators (1991) studied the relationship between parental smoking and incidence of lower respiratory tract illnesses in the first year of life in a cohort of 847 white, non-Hispanic infants from Tucson, Arizona, who were enrolled at birth and followed prospectively. Lower respiratory illnesses were diagnosed by the infants' pediatricians. Maternal and paternal smoking was ascertained by questionnaire. For verification of smoking habits, the researchers measured cotinine in umbilical cord serum of a sample of 133 newborns who were representative of the population as a whole. Cotinine was detectable in umbilical cord sera of all infants whose mothers reported smoking during pregnancy and in 7 of 100 cord specimens of infants whose mothers said they had not smoked during pregnancy. There was a strong relationship between cotinine level at birth and the amount that the mother reported having smoked during pregnancy.

Children whose fathers smoked were no more likely to have a lower respiratory tract illness in the first year of life than were children of nonsmoking fathers (31.3% vs. 32.2%, respectively). The incidence of lower respiratory tract illnesses was 1.5 times higher (95% C.I. = 1.1-2.2) in infants whose mothers smoked as in infants whose mothers were nonsmokers. This relationship became stronger when mothers who were heavy smokers were separated from light smokers; 45.0% of children born to mothers who smoked > 20 cigarettes per day had a lower respiratory illness, compared to 32.1% of children whose mothers smoked 1 to 19 cigarettes per day and 30.5% of children of nonsmoking mothers ($p < 0.05$). The authors tried to differentiate

250103199

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

the effects of maternal smoking during pregnancy from those of postnatal exposure to ETS but concluded that the amount smoked contributed more to lower respiratory tract illness rates than did the time of exposure. The authors also found that maternal smoking had a significant effect on the incidence of lower respiratory tract illnesses only for the first 6 months of life; the risk of having a first lower respiratory illness between 6 and 12 months was independent of maternal smoking habits. A logistic regression showed that the effect of maternal smoking was independent of parental childhood respiratory troubles, season of birth, day-care use, and room sharing. Feeding practices, maternal education, and child's gender were unrelated to incidence of lower respiratory illnesses in this sample and were not included in the regression. The analysis also showed a significant interaction between maternal smoking and day-care use; the effects of maternal smoking were significant when the child did not use day care (OR = 2.7; 95% C.I. = 1.2-5.8) but were weaker and did not reach significance among infants who used day care (OR = 1.9; 95% C.I. = 0.9-4.0). The authors suggested that day-care use may protect against lower respiratory illnesses by reducing exposure to ETS.

7.3.2. Summary and Discussion on Acute Respiratory Illnesses

Both the literature referenced in the Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) and the additional, more recent studies considered in this report provide strong evidence demonstrating that children who are exposed to ETS in their home environment are at considerably higher risk of having acute lower respiratory tract illnesses than are unexposed children. Increased risk associated with ETS exposure has been found in different locales, using different methodologies, and in both inpatient and outpatient settings. The effects are biologically plausible (see Section 7.2). Several studies have also reported a dose-response relationship between degree of exposure (as measured by number of cigarettes smoked in the household) and risk of acute respiratory illnesses. This also supports the existence of a causal explanation for the association.

The majority of studies found that the effect was stronger among children whose mothers smoked than among those whose fathers smoked. This is further evidence in favor of a causal explanation, because infants are generally in closer, more frequent, contact with their mothers. There are now also fairly convincing data showing that the increased incidence of acute respiratory illnesses cannot be attributed exclusively to in utero exposure to maternal smoke. In fact, Chen and coworkers (1986, 1988, 1989) reported increased risk of acute respiratory illnesses in Chinese children living with smoking fathers and in the total absence of smoking mothers. This effect could also be attributed either to in utero exposure to the father's smoke or to an effect on

25010319997

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

the father's sperm. This seems unlikely, however, because no such effects of parental smoking during pregnancy have been described in similar studies performed in western countries. Furthermore, Woodward and coworkers (1990) found that children of smoking mothers were significantly more prone to acute respiratory illnesses even after mothers who smoked during pregnancy were excluded from the analysis. This clearly suggests the existence of direct effects of ETS exposure on the young child's respiratory health that are independent of in utero exposure to tobacco smoke products.

There is also convincing evidence that the risk is inversely correlated with age; infants aged 3 months or less are reported to be 3.3 times more likely to have lower respiratory illnesses if their mothers smoke 20 cigarettes per day or more than are infants of nonsmoking mothers (Wright et al., 1991). Increases in incidence of 50% to 100% (relative risks of 1.5-2.0) have been reported in older infants and young children. The evidence for an effect of ETS is less persuasive for school-age children, although trends go in the same direction as those reported for younger children. This may be due to a decrease in illness frequency, to physiological development of the respiratory tract or immune system with age, or to a decreased contact between mother and child with age.

Reasonable attempts have been made in most studies to adjust for a wide spectrum of possible confounders. The analyses indicate that the effects are independent of race, parental respiratory symptoms, presence of other siblings, socioeconomic status or parental education, crowding, maternal age, child's sex, and source of energy for cooking. One study (Graham et al., 1990) also showed that the effect of ETS exposure on proneness to acute respiratory illnesses in infancy and early childhood was also independent of several indices of maternal stress, lack of maternal social support, and family dysfunction. Other factors, such as breastfeeding, decreased birthweight, and day-care attendance, have been shown to modify the risk.

Some sources of bias may have influenced the results, but it is highly unlikely that they explain the consistent association between acute lower respiratory illness and ETS exposure. With one exception (Wright et al., 1991), all studies relied exclusively on questionnaires or interviews to assess exposure. Although questions tend to be very specific, overreporting or more accurate reporting of smoking habits by parents of affected children is possible, particularly in case-control and retrospective studies. However, such a bias should affect both respiratory and nonrespiratory outcomes, and at least two studies have shown no association between nonrespiratory outcomes and ETS exposure (Chen et al., 1988; Breese-Hall et al., 1984). Selection bias could not be excluded in some case-control studies, but satisfactory efforts were made to avoid this source of bias in most studies.

250103 1998

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

7.4. PASSIVE SMOKING AND ACUTE AND CHRONIC MIDDLE EAR DISEASES

The Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) reviewed five studies demonstrating an excess of chronic middle ear disease in children exposed to parental cigarette smoke (Table 7-3). Both reports conclude that the data are consistent with increased rates of chronic ear infections and middle ear effusions in children exposed to ETS at home.

7.4.1. Recent Studies on Acute and Chronic Middle Ear Diseases

Several recent studies not referenced in the Surgeon General's report or in the NRC report have addressed the relationship between parental smoking and middle ear illnesses in children (Table 7-4).

Fleming and coworkers (1987) examined retrospectively risk factors for the acquisition of infections of the upper respiratory tract in 575 children less than 5 years of age. Information on smoking habits and on upper respiratory tract infections and ear infections in the 2 weeks prior to interview was obtained from the child's guardian. The authors reported a 1.7-fold increase ($p = 0.01$) in the risk of having an upper respiratory illness in children of smoking mothers when compared to children of nonsmoking mothers. This effect was independent of feeding practices, family income, crowding, day-care attendance, number of siblings aged less than 5 years, child's age, and race. The authors calculated that 10% of all upper respiratory illnesses in the population were attributable to maternal smoking, a proportion that was comparable to that attributable to day-care attendance. There was no relationship between maternal smoking and frequency of ear infections in this population sample.

Willatt (1986) studied 93 children who were the entire group of children admitted to a Liverpool hospital for tonsillectomy (considered an index of frequent upper respiratory or ear infections) during a 3-month period, and 61 age- and sex-matched controls. The median age was 6.9 years (range 1.8-14.9). Parents were asked the number of sore throats in the previous 3 months and the smoking habits of all members of the household. There was a significant relationship ($p < 0.05$) between number of episodes of sore throat and number of cigarettes smoked by the mother. The effect was independent of birthweight, sex, child's age, feeding practices, social class, crowding, and number of sore throats and tonsillectomies in other household members. The relative odds of having a smoking mother were 2.1 times as high (95% C.I. = 1.1-4.0) in children about to undergo tonsillectomy as in children not undergoing tonsillectomy.

Tainio and coworkers (1988) followed 198 healthy newborns from birth to 2.3 years of age. They recorded physician-diagnosed recurrent otitis media (defined as more than four episodes of

25010319 99

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

otitis media during the first 2 years or more than four episodes during the second year). Parental smoking was more frequent (55%) among the infants with recurrent otitis media than in the comparison group (33%; $p < 0.05$). The authors comment, however, that "parental smoking was not a risk factor for recurrent otitis media," probably because there was no significant relationship between parental smoking and recurrent otitis media using definitions of the latter that differed from the one described above. No distinction was made in this study between the possible effects of maternal and paternal smoking. In addition, the study sample was probably too small to obtain reliable risk calculations.

Reed and Lutz (1988) studied 24 out of 70 eligible children who had been seen in a family practice office for acute otitis media during a period of 4 months, and 25 out of 70 eligible children who had been seen for other reasons. Forty-five of these children had tympanograms performed and also had information on household smoke exposure. Prevalence of an abnormal tympanogram (indicating the presence of middle ear effusion) was higher among children exposed to smokers at home (OR = 4.86, 95% C.I. = 1.4-17.2). Results were independent of feeding practices, history of upper respiratory illness in the past month, low socioeconomic status, sex, age, and attendance at a day-care center. Only a small fraction of eligible subjects were included in this study, and the possibility of selection bias as an explanation for the reported results cannot be ruled out.

Hinton (1989) compared 115 children aged 1 to 12 years (mean = 5 years) admitted to a British hospital for grommet insertion with 36 children aged 2 to 11 (mean = 6 years) with normal ears who were taken from an orthoptic clinic. Prevalence of smoking was significantly higher in parents of cases than in parents of controls (OR = 2.1, 95% C.I. = 1.0-4.5). Potential sources of selection bias or selective misclassification cannot be determined from the data reported by the author. No effort was made to control for possible confounders.

Teele and coworkers (1989) studied consecutively enrolled children being followed in two health centers in Boston from shortly after birth until 7 years of age. Acute otitis media and middle ear effusion were diagnosed by the child's pediatrician. Data were analyzed for 877 children observed for at least 1 year, 698 children observed for at least 3 years, and 498 children observed until 7 years of age. A history of parental smoking was obtained when each child became 2 years old. A parent was considered a smoker if he or she smoked more than one cigarette per day. The child was considered exposed if either parent was a smoker. The authors reported that the incidence of acute otitis media during the first year of life was 13% higher in children of smoking parents when compared to children of nonsmoking parents ($p < 0.05$), but statistical significance was no longer present after controlling for alleged confounders (site of

25010320000

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

health care, season of birth, birthweight, socioeconomic status, presence and number of siblings, room sharing, feeding practices, sibling or parental history of ear infection and allergic diseases). Several of these variables could have not been confounders if they were not related to both parental smoking and incidence of acute otitis media. Controlling for risk factors that are not confounders may result in overcorrection. Parental smoking was not associated with an increased risk for acute otitis media during the first 3 years or 7 years of life. Likewise, parental smoking was associated with a significant increase in the number of days with middle ear effusion, but only during the first year of life ($p < 0.009$), and the effect was no longer present after alleged confounders were controlled for. The authors do not provide information on separate risks for maternal and paternal smoking or on the incidence of acute otitis media and middle ear effusion in children of heavy smokers.

Takasaka (1990) performed a case-control study on 201 children aged 4 to 8 in Sendai, Japan. Sixty-seven subjects had otitis media with effusion, and the remaining 134 children were a control group matched to cases by age, sex, and kindergarten class. The investigators found no significant differences in prevalence of exposure to two or more household cigarette smokers between children with and without otitis media with effusion (no information on either odds ratios or C.I.s is given). The power of this study may have been too low to determine risk factors for middle ear effusions reliably.

Corbo and coworkers (1989) examined 1,615 children aged 6 to 13 years who shared a bedroom with siblings or parents in Abruzzo, Italy. Parents were asked if the child snored and the frequency of snoring. Parents were asked about their own smoking habits; they were considered moderate smokers if the summed total for both parents was fewer than 20 cigarettes per day and heavy smokers if the summed total was 20 or more cigarettes per day. Prevalence of habitual snoring in children increased slightly with the amount of cigarettes smoked by parents; children of heavy smokers were 1.9 times as likely to be habitual snorers as children in nonsmoking households (95% C.I. = 1.2-3.1), whereas children of moderate smokers were 1.8 times as likely to be habitual snorers as children of nonsmoking parents (95% C.I. = 1.1-3.0). Habitual snorers were more likely to have had a tonsillectomy, but only if their parents smoked. The authors suggested that these results are plausible because adult smokers are also at increased risk of being habitual snorers.

Strachan and collaborators (1989) performed tympanograms and collected saliva for cotinine determinations in 736 children in the third primary class (ages 6½ to 7½ years) in Edinburgh, Scotland. Median of salivary cotinine concentrations was 0.19 ng/mL for 405 subjects living with no smoker, 1.8 ng/mL for 241 subjects living with one smoker, and 4.4 ng/mL for 124

250103200

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

subjects living with ≥ two smokers. For a given number of smokers in the household, girls had higher cotinine levels than boys and children living in rented houses (i.e., of lower socioeconomic level) had higher cotinine levels than children living in houses owned by their parents. The authors found a linear relation between the logarithm of the salivary cotinine concentration and the prevalence of middle ear effusion. The authors calculated odds ratios for abnormal tympanometry relative to children with undetectable cotinine concentrations, after adjustment for sex, housing tenure (rented or owned), social class, crowding, gas cooking, and the presence of damp walls. The odds ratio for a doubling of salivary cotinine concentration was 1.14 (95% C.I. = 1.03-1.27). At a salivary cotinine concentration of 1 ng/mL, the odds ratio of having an abnormal tympanogram was 1.7, whereas an odds ratio of 2.3 was calculated for a cotinine level of 5 ng/mL. At least one-third of all cases of middle ear effusion may have been attributable to passive smoking.

7.4.2. Summary and Discussion of Middle Ear Diseases

There is some evidence suggesting that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies have failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

Available data provide good evidence demonstrating a significant increase in the prevalence of middle ear effusion in children exposed to ETS. Several studies in which no significant association was found between ETS exposure and middle ear effusion were not specifically designed to test this relationship, and, therefore, either power was insufficient or assessment of the degree of exposure was inadequate. Also, Iversen and coworkers (1985), who assessed middle ear effusion objectively, suggested that the risk associated with passive smoking increased with age. This may explain the negative results of several studies based on preschool children; the sample sizes of these studies may have been inadequate to test for increased risks of 50% or less, as would be expected in children < 6 years of age. The finding of a log-linear dose-response relationship between salivary cotinine levels and the prevalence of abnormal tympanometry in one study (Strachan et al., 1989) adds to the evidence favoring a causal link. Although not all studies adjusted for possible confounders, and selection bias cannot be excluded in the case-control studies reviewed, the evidence as a whole suggests that the association is not likely to be due to chance, bias, or factors related to both ETS exposure and middle ear effusion.

25010320002

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The biological mechanisms explaining the association between ETS exposure and middle ear effusion require further elucidation. Otitis media with effusion is usually attributed to a loss of patency of the eustachian tube, which may be enhanced by upper respiratory infection, impaired mucociliary function, or anatomic factors (see Strachan et al., 1989). It is possible that pharyngeal narrowing by adenoidal tissue (and, consequently, eustachian tube dysfunction) may be more common in these children. This is suggested by reports of a higher prevalence of maternal smoking among children about to undergo or who have undergone tonsillectomy and by an increased prevalence of habitual snoring among children of smoking parents. Impaired mucociliary clearance has been convincingly demonstrated in smoking adults (U.S. DHHS, 1984). No data are available on mucociliary transport in children exposed to ETS. However, ETS may affect mucociliary clearance in children as in adults. If this were the case, and if normal mucociliary clearance is required for rapid resolution of otitis media, exposure to ETS could result in increased prevalence of chronic middle ear effusion.

The increased prevalence of middle ear effusion attributable to ETS exposure has very important public health consequences. Middle ear effusion is the most common reason for hospitalization of young children for an operation, and thus imposes a heavy financial burden to the health-care system (Black, 1984). There is also evidence suggesting that hearing loss associated with middle ear effusion may have long-term consequences on linguistic and cognitive development (Maran and Wilson, 1986).

7.5. EFFECT OF PASSIVE SMOKING ON COUGH, PHLEGM, AND WHEEZING

Studies addressing the effects of passive smoking on frequency of chronic cough, phlegm, and wheezing were reviewed both in the Surgeon General's report (U.S. DHHS, 1986) and in the report by the NRC (1986) (see Table 7-5).

The Surgeon General's report concluded that children whose parents smoke were found to have 30% to 80% excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over sixfold among the studies reviewed. The report noted that the association with parental smoking was not statistically significant for all symptoms in all studies, but added that the majority of studies showed an increase in symptom prevalence with an increase in the number of smoking household members in the home. The report stated that the results of some studies could have been confounded by the child's own smoking habits, but noted that many studies showed a positive association between parental smoking and symptoms in children at ages before significant experimentation with cigarettes is prevalent. The report concluded that "chronic cough and

25010320

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

phlegm are more frequent in children whose parents smoke compared to nonsmokers. The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study" (page 107).

The NRC report concluded that "children of parents who smoke compared with children of parents who do not smoke show increased prevalence of respiratory symptoms, usually cough sputum and wheezing. The odds ratios for the larger studies, adjusted for the presence of parental symptoms, were 1.2-1.8, depending on the symptoms. These findings imply that ETS exposures cause respiratory symptoms in some children" (page 216).

7.5.1. Recent Studies on the Effect of Passive Smoking on Cough, Phlegm, and Wheezing

Several recent studies not considered either in the NRC report (1986) or in the Surgeon General's report (U.S. DHHS, 1986) have addressed the relationship between passive smoking and respiratory symptoms in children (Table 7-6).

McConnochie and Roghmann (1986b) studied 223 out of 276 eligible children aged 6 to 10 years without a history of bronchiolitis who were drawn from the patient population of a group practice in Rochester, New York. Information regarding the child's history of wheezing in the previous 2 years, socioeconomic status, family history of respiratory illnesses, and smoking in the household was obtained by questionnaire. Information on breastfeeding was obtained by record checks and interviews. Children whose mothers smoked were more likely to be current wheezers than were children whose mothers did not smoke (OR = 2.2, 95% C.I. = 1.0-4.8). Neither paternal smoking nor total household smoking had any influence on the prevalence of wheezing. When the authors controlled for family history of respiratory allergy, direct effects of maternal smoking on prevalence of wheezing failed to reach statistical significance. However, there was a strong association between maternal smoking and wheezing among children with a positive family history of respiratory allergy (OR = 4.5, 95% C.I. = 1.7-12.0), and the interaction between these terms was highly significant in multivariable analysis, suggesting the combined importance of both genetic factors and maternal smoking.

Park and Kim (1986) studied 3,651 children aged 0 to 14 from a randomized, clustered sample of households in South Korea (response rate: 89%). A questionnaire was administered to household members about their smoking habits and respiratory symptoms. Mothers answered questions about the presence of cough in the child in the 3 months prior to interview. The authors reported dose-response relationships between the child's cough and number of smokers in the family, number of smokers in the same room, number of cigarettes smoked by all family members, and number of cigarettes smoked by parents. The relationship was present in children

250103200H

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

of different ages (less than 5 years, 6 to 11 years, and 12 to 14 years). The authors controlled for parental education, socioeconomic status, birth rank, parental age, birth interval, number of family members, and number of siblings. Family members with cough or with morning phlegm production were significantly more likely to live with children with cough. After correcting for these two factors, chronic cough was 2.4 times as likely in children of families whose members smoked 1 to 14 cigarettes per day (95% C.I. = 1.4-4.3) and 3.2 times as likely in children of families whose members smoked more than 15 cigarettes per day (95% C.I. = 1.9-5.5). However, effects were more noticeable and only reached statistical significance in children of families whose adult members did not have chronic cough.

Bisgaard and coworkers (1987) studied 5,953 infants out of a total of 8,423 eligible newborns (71%) enrolled in a prospective study. At the age of 1 year, the child's mother was interviewed regarding episodes of wheeze during the previous year and possible risk factors for wheezing. The risk of wheezing was 2.7 times as high (95% C.I. = 1.8-4.0) in children whose mothers smoked $\geq$ 3 cigarettes per day as in children whose mothers smoked < 3 cigarettes per day. Results were independent of social status and sex of the child. The authors decided not to control for quarter of birth or use of day-care facilities, with the assumption that these factors did not modify the relationship between maternal smoking and wheezing. Also, biases could have been introduced by the fact that almost one-third of the original sample was not included in the analysis.

Geller-Bernstein and coworkers (1987) studied 80 children aged 6 to 24 months who had been seen as outpatients or inpatients in Israel for wheezing and who had a diagnosis of atopy. The children were examined every 6 months during 4 years by a physician. At the end of assessment, the authors classified children as having "recovered" if they had been symptom-free for at least 1 (the last) year; otherwise they were classified as "persistent wheezers." "Persistent wheezers" were more likely to have smoking parents than were "recovered" children (OR = 3.1, 95% C.I. = 1.1-8.9). This result was independent of changes in IgE levels during the study period. The authors did not control for the possible confounding effect of parental symptoms.

Cogswell and coworkers (1987) studied 100 newborns who had at least one parent with a history of hay fever or asthma. Ninety-two children were still being followed at 1 year of age and 73 at the age of 5 years. Children were examined periodically and whenever they had signs of respiratory illness. At the child's first birthday, the number of those who had developed wheezing was equally distributed between parents who did or did not smoke. By the age of 5 years, however, 62% of parents who smoked had children who had wheezed compared with 37% in nonsmoking families ($p < 0.05$). It is unlikely that these results can be explained by the

250103200S

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

confounding effect of parental symptoms, because all parents were allergic by definition. It is also quite unlikely that preferential withdrawal of nonwheezing children of smoking parents could have biased the results.

Toyoshima and coworkers (1987) from Osaka, Japan, followed 48 out of 65 wheezy infants and children less than 3 years old for up to 4 years. Outcome information was obtained from charts or by telephoning the child's mother. Among 18 children who were still symptomatic 25 to 44 months after their first visit, 17 lived with smokers, compared to 13 of 22 children who lived with smokers and who stopped having symptoms during follow-up (OR = 11.8, 95% C.I. = 1.3-105.0). Results were independent of family history of allergy, feeding practices, and disturbances at birth. Selection bias related to the number of subjects lost for follow-up or with missing information could have influenced the results of this study.

Tsimoyianis and collaborators (1987) evaluated the effects of exposure to ETS on respiratory symptoms in a group of 12- to 17-year-old high school athletes (N = 193). Histories of smoking by all household members were obtained for all subjects. Athletes exposed to ETS at home were more likely to report cough than were unexposed athletes ($p = 0.08$). Frequency of bronchitis, wheeze, and shortness of breath were similar in both groups. A greater awareness of the smoking habits of those around them by subjects with cough cannot be excluded as an explanation of these findings, but this source of bias cannot explain the exposure-response trends for ETS and lung function seen in this same sample (see Section 7.7.1).

Andrae and collaborators (1988) mailed questionnaires to the parents of 5,301 children aged 6 months to 16 years living in the city of Norrkoping, Sweden. Data were obtained from 4,990 children (94% response rate). Children with parents who smoked had exercise-induced cough more often than did children of nonsmokers (OR = 1.4, 95% C.I. = 1.1-1.8). Exposure to ETS interacted with living in houses with damage by dampness; children exposed to both had more exercise-induced cough and allergic asthma when compared to those exposed to only one or neither. Results of this cross-sectional study may have been biased by preferential reporting of symptoms by smoking parents, although a reliability study performed in a random sample was reported to confirm 95% of the answers regarding respiratory symptomatology. In addition, no effort was made to control for active smoking in older children.

Somerville and coworkers (1988) enrolled 88% of 8,118 eligible children aged 5 to 11 from England and Scotland. Data on the child's respiratory symptoms and parental smoking were obtained from a self-administered questionnaire completed by the child's mother. After exclusions for missing data, the proportions of children available ranged from 60.9% to 63.9% of all subjects, depending on the variables involved. Logistic regression analysis was used to control

250103200G

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

for child's age, presence of siblings, one- or two-parent families, paternal employment, social class, maternal smoking during pregnancy, overcrowding, maternal education, maternal age, triceps skinfold thickness, and birthweight. For Scottish children (who were only 19% of all subjects), the authors found a significant relationship between number of cigarettes smoked at home and "chest ever wheezy" ($p < 0.01$; OR not reported). Among English children, there was a significant relationship between number of cigarettes smoked at home by mother and father together and prevalence of a wheezy or whistling chest most nights (adjusted OR in children whose parents smoked 20 cig./day = 1.6; 95% C.I. = 1.2-2.2). Attacks of bronchitis and cough during the day or at night were also significantly correlated with number of cigarettes smoked by parents in the English sample; odds ratios in children of parents who smoked 20 cigarettes per day were 1.4 and 1.3, respectively, but no confidence intervals were reported. The authors concluded that the effect of parental smoking on respiratory symptoms in this age group is small and requires a large number of subjects to be detected.

Rylander and collaborators (1988) from Stockholm, Sweden, studied 67 children aged 4 to 7 years who had been hospitalized with virologically proven RSV infections before age 3. Questionnaires were mailed to parents regarding their smoking habits and the child's history of wheezing illnesses after the initial episode. Children who had subsequent occasional wheezing (n = 21) were more likely to have smoking parents than those (n = 24) who had no subsequent respiratory symptoms (OR = 4.3, 95% C.I. = 1.1-16.4). However, frequency of parental smoking among children who had no subsequent respiratory symptoms was not significantly different from that of children who had subsequent recurrent wheezing. The inconsistency of the results in this study may be explained by the small number of subjects involved.

Strachan (1988) studied 1,012 out of a target sample of 1,095 schoolchildren aged 6.5 to 7.5 years in Edinburgh, Scotland. Parents answered a questionnaire on their smoking habits and on respiratory symptoms in their children. There was no relationship between number of smokers in the household and prevalence of wheezing in the population. Cough at night (> 3 nights in the past month) was more likely to occur in children living with one smoker (OR = 1.6; 95% C.I. = 1.1-2.6) or two smokers (OR = 2.5; 95% C.I. = 1.5-4.0) than in children living with nonsmokers. Occurrence of "chesty colds" in children was also more frequent in households with one (OR = 1.3; 95% C.I. = 0.9-1.9) or two smokers (OR = 1.9; 95% C.I. = 1.3-3.0).

A subsequent report (Strachan et al., 1990) based on the same population sample studied the relationship between salivary cotinine levels and respiratory symptomatology in a subset of 770 children (see also Strachan et al. [1989]), Section 5.4.1). The authors found no relationship between cotinine levels and wheezing or frequent night cough. Frequency of chesty colds was

250103200?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

significantly correlated with quintals of salivary cotinine ($p < 0.01$). The authors noted that objective markers of recent exposure to ETS may not adequately reflect exposure at some critical period in the past. They also noted that there may be different ways of understanding the concept of "wheezing" and proposed that this could explain the lack of association between this symptom and both questionnaire-based and cotinine-based assessment of exposure to ETS in their sample.

Lewis and coworkers (1989) performed a case-control study of risk factors for chronic cough in children under 6 years in Salford, United Kingdom. They enrolled 60 children referred to a pediatric outpatient clinic with cough lasting more than 2 months or frequent episodes of cough without wheeze. These 60 subjects were compared with controls admitted for routine surgical procedures. Children with chronic cough were 1.7 times (95% C.I. = 0.8-3.5) as likely to live with a smoker as were controls. Because of the small number of subjects and the high prevalence of parental smoking (> 50%), the power of this study may have been too low to allow for meaningful conclusions.

Neuspiel and coworkers (1989) studied 9,670 out of 9,953 eligible children enrolled at birth in Great Britain. Information on parental smoking was obtained at birth, at age 5 years, and at age 10 years. Outcome data were obtained from maternal interviews when the children were 10 years old. Children of smoking mothers had 11% higher risk (95% C.I. = 2%-21%) of wheezing between ages 1 and 10 than did children of nonsmoking mothers. An exposure-response relationship was also present: Cumulative incidence was 5.2% in children whose mothers were nonsmokers, 6.6% in children whose mothers smoked 1 to 4 cigarettes per day, 7.5% in children whose mothers smoked 5 to 14 cigarettes per day, 8.1% in children whose mothers smoked 15 to 24 cigarettes per day, and 8.9% in children whose mothers smoked > 24 cigarettes per day. The risk was also increased in children of mothers who did not smoke during pregnancy but were smokers thereafter (RR = 2.2, 95% C.I. = 1.2-3.9). The association persisted after a logistic regression model was used to control for the effect of child's sex, child allergy, paternal smoking, parental allergy, crowding, bedroom dampness, feeding practices, gas cooking, and social status. The increase in risk was cut approximately in half but did not disappear when additional corrections for maternal respiratory symptoms and for a measure of maternal depression were made. Results of this study may be explained in part by preferential reporting of wheezy illnesses by smoking mothers. However, it is unlikely that the association between maternal smoking and wheezy illnesses found in this study can be exclusively explained by uncontrolled sources of bias; there was a striking exposure-response effect and the association persisted after controlling for most known confounders and was independent of maternal smoking during pregnancy.

2501032008

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Chan and collaborators (1989) studied 134 children aged 7 years out of 216 eligible infants of under 2,000 g birthweight who were admitted to the neonatal unit of two hospitals in London, England. Parents of each of these 134 cases and of 123 control schoolchildren born in the same period but with normal birthweight completed a self-administered questionnaire on respiratory illnesses and on social and family history. At age 7, children whose mothers smoked were at increased risk of having frequent wheeze independent of their neonatal history (adjusted OR = 2.7; 95% C.I. = 1.3-5.5), although the increase only reached statistical significance for children of normal birthweight. Prevalence of frequent cough was also more likely to occur in children of smoking mothers (OR = 2.4, 95% C.I. = 1.3-4.6), and the association was significant for both cases and controls studied separately. The authors performed a logistic regression to control for possible confounders (only the low birthweight group was included). The relationship between frequent wheeze and maternal smoking persisted among low-birthweight children after controlling for family history of asthma, atopy, socioeconomic status, and use of neonatal oxygen. The relationship between frequent cough and maternal smoking was no longer significant among low-birthweight infants after controlling for the same possible confounders. For the low-birthweight group, the authors assessed the reliability of some of the responses to their questionnaires; there was a high correlation (r = 0.96) between the number of hospitalizations reported by parents and those documented in the outpatient clinic of the neonatal unit that followed the infants. The authors concluded that misclassification due to parental failure to recall previous respiratory illnesses in the low-birthweight group was unlikely.

Krzyzanowski and collaborators (1990) studied a sample of 298 children aged 5 to 15 who were family members of county employees enrolled in a prospective study. Parents answered a questionnaire on their smoking habits and on respiratory symptoms in their children. Indoor formaldehyde concentrations in the living environment were also measured. Prevalence rates of chronic bronchitis (as diagnosed by a physician) were significantly higher in children exposed both to ETS and to formaldehyde concentrations of over 60 parts per billion than in children with one or none of these exposures. The authors also reported that similar effects were not seen in adults.

Dijkstra and collaborators (1990) obtained consent for participation in their study for 1,051 out of a total of 1,314 (80%) eligible 6- to 12-year-old schoolchildren from a rural area in The Netherlands. Parents completed a self-administered questionnaire on their smoking habits and on respiratory symptoms in their children. Complete information was available for 775 children. When compared to children of nonsmoking households, children exposed to ETS at home were significantly more likely to have cough on most days for at least 3 months

250103200

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

consecutively (OR = 2.5, 95% C.I. = 1.1-5.6); wheezy or whistling sounds in the chest in the last year (OR = 1.9; 95% C.I. = 1.0-3.5), and attacks of shortness of breath with wheeze in the last year (OR = 2.0; 95% C.I. = 0.9-4.2). Exposed children were significantly more likely to have one or more of the above symptoms than were unexposed children (OR = 2.0; 95% C.I. = 1.2-3.7). Results were still significant after adjusting for parental respiratory symptoms and for maternal smoking during pregnancy. The authors also measured nitrogen dioxide in the homes of all children but found no association of the latter with respiratory symptoms.

Mertsola and coworkers (1991) followed prospectively for 3 months 54 patients aged 1 to 6 years from Turku, Finland, who had a history of recurrent attacks of wheezy bronchitis. The parents were told to record the symptoms of the child daily and were asked to bring their child to the hospital emergency room if the child developed signs of an acute respiratory infection. Incidence of prolonged wheezing episodes (> 4 days) during follow-up was significantly more likely in children exposed to ETS than in unexposed children (OR = 4.8; 95% C.I. = 1.9-12.6). The result was independent of number of siblings, age, sex, medication, and personal history of allergy.

7.5.2. Summary and Discussion on Cough, Phlegm, and Wheezing

Recent studies reviewed in this report that were not included either in the Surgeon General's report (U.S. DHHS, 1986) or in the NRC report (1986) substantially confirm the conclusions reached in those two reports. There is sufficient evidence for the conclusion that ETS exposure at home is causally associated with respiratory symptoms such as cough, phlegm, or wheezing in children.

The evidence is particularly strong for infants and preschool children; in this age range, most studies have found a significant association between exposure to ETS (and especially to maternal smoking) and respiratory symptoms in their children, with odds ratios generally ranging between 1.2 and 2.4. Selection bias may have influenced the results of certain cross-sectional studies; retrospective studies may also have been biased by preferential recall of their children's symptoms by smoking parents. However, the presence of a causal relationship is strongly supported by the consistency of the results for different geographic areas (Japan, Korea, People's Republic of China, Europe, and North America) and by the positive findings in prospective studies that are less subject to selection and recall biases.

In addition, efforts have been made by all researchers to control for possible confounders and to avoid sources of bias. It is not feasible for each study to take into account all possible factors that may affect the relationship under study; some of these factors may even be unknown

250103201O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

at present. However, all reviewed studies have controlled for at least some of the best-known confounders (family history of respiratory illnesses, parental respiratory symptoms, socioeconomic status, crowding, presence of other siblings, home dampness, gas cooking, maternal level of education, perinatal problems, low birthweight, maternal age, birth rank, maternal stress or depression). Of these possible confounders, a history of respiratory symptoms in parents has been particularly scrutinized. The NRC report (1986) noted that bias may be introduced by parents who have a history of respiratory illnesses for several reasons. These parents may overstate their children's symptoms, or their children may actually have more respiratory illnesses and symptoms. The latter possibility could be the result of intrafamily correlation of susceptibility (referred to as familial resemblance by Kauffmann and coworkers [1989a]). Because smokers are more likely to have respiratory symptoms, one would expect that controlling for respiratory symptoms in parents would result in a decrease in statistical significance of the relationship between ETS and symptoms in the child. In fact, most recent studies that have addressed the issue report that controlling for family history of respiratory symptoms decreases but does not entirely explain the increased risk of respiratory symptoms in young children exposed to ETS. It has been stressed, however, that the use of these statistical adjustment procedures may induce an underestimation of the effect of passive smoking; this would indeed be the case if parents with symptoms (and thus more likely to be smokers) were more prone to report symptoms in their children than were parents without symptoms. Several studies have also found that the effect is independent of maternal smoking during pregnancy and cannot be attributed exclusively to intrauterine exposure to tobacco products (although the latter may potentiate the effects of postnatal exposure to ETS).

The evidence is significant but less compelling for a relationship between exposure to ETS and respiratory symptoms in school-age children. Odds ratios for this age group are usually between 1.1 and 2.0. Several studies have shown that, among school-age children, there are significant differences in susceptibility to ETS exposure between individuals. There is, in fact, evidence showing that several factors may amplify the effects of passive smoking: prematurity, a family history of allergy, a personal history of respiratory illnesses in early childhood, and being exposed to other environmental pollutants such as formaldehyde. In addition, long-term exposure may have more important effects than short-term exposure. One study of 7-year-old children (Strachan, 1988; Strachan et al., 1990) used both questionnaires regarding smoking habits in the household and the child's saliva cotinine levels as indices of exposure to ETS. The authors found a significant increase in the risk of having frequent cough when the questionnaire was used to ascertain exposure, but no association between saliva cotinine levels and frequency of cough. As the authors remarked, biochemical markers permit characterization of recent tobacco smoke

250103201 1

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

exposures, but they may not adequately reflect exposure at some critical period in the past. Recent studies of intraindividual variability of cotinine levels have also suggested that it may be misleading to assess the validity of questionnaire measures against a single determination of a biologic marker (Coultas, 1990b; Idle, 1990). It is thus possible that associations evaluated with salivary cotinine are likely to underestimate the true relationship between passive smoking and respiratory morbidity (Strachan et al., 1990).

In the case of older children who may have started experimenting with cigarettes, the confounding effects of active smoking need to be considered. Most researchers have been aware of this problem and have attempted to control for it. A great difficulty lies in misclassification of smokers due to underreporting. Young persons may be reluctant to admit smoking cigarettes. Data are often obtained from parents, who may not be aware of the child's smoking.

In summary, this report concludes that ETS exposure at home causes increased prevalence of respiratory symptoms in infants and young children. There is also good evidence indicating that passive smoking causes respiratory symptoms in some older children, particularly in children who have predisposing factors that make them more susceptible to the effects of ETS.

7.6. EFFECT OF PASSIVE SMOKING ON ASTHMA

Studies addressing the effects of passive smoking on frequency of asthma were directly reviewed only in the Surgeon General's report (U.S. DHHS, 1986) and not explicitly in the report on environmental tobacco smoke by the NRC (1986). The Surgeon General's report concluded that epidemiologic studies of children had shown no consistent relationship between the report of a doctor's diagnosis of asthma and exposure to involuntary smoking. The report pointed out that, although one study had shown an association between involuntary smoking and asthma (Gortmaker et al., 1982), others had not (Schenker et al., 1983; Horwood, 1985). This variability was attributed to differing ages of the children studied, differing exposures, or uncontrolled bias. The report also concluded that maternal cigarette smoking may influence the severity of asthma. Alteration of nonspecific bronchial responsiveness was proposed as a mechanism for this latter effect.

7.6.1. Recent Studies on the Effect of Passive Smoking on Asthma in Children

Several new cross-sectional and longitudinal studies published after the U.S. Surgeon General's report was released have addressed the relationship between frequency, incidence, and severity of asthma and parental cigarette smoke (Table 7-7). (Studies on the relationship between ETS exposure and bronchial responsiveness were reviewed in Section 7.1.4.)

250103201 2

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Burchfiel and coworkers (1986) studied 3,482 nonsmoking children and adolescents 0 to 19 years of age out of 4,378 eligible subjects from Tecumseh, Michigan. Subjects or their parents (for children aged 15 years or younger) answered questionnaires on past history of asthma and other respiratory conditions. Information on parental smoking habits was obtained from each parent. Prevalence rates of asthma were higher among children whose parents both had smoked during the child's lifetime than among children whose parents had never smoked. The effect was stronger and only reached statistical significance for males (OR for boys = 1.7, 95% C.I. = 1.2-2.5 in boys; OR for girls = 1.2, 95% C.I. = 0.8-1.9). Children with one parental smoker were not more likely to have asthma than was the unexposed reference group. When results were stratified by parental history of respiratory conditions, there was some reduction in the magnitude of the parental smoking effects, but results remained significant for asthma in males. Results were also independent of age, parental education, family size, a diagnosis of hay fever, and a history of other allergies. Reporting bias and diagnostic bias may in part explain the relationships reported in this study; smoking parents may be more likely to report asthma in their children, and physicians may be more prone to diagnose asthma in children of smoking parents.

Evans and coworkers (1987) studied 191 out of 276 children aged 4 to 17 years from low-income families who were receiving health care for physician-diagnosed asthma in New York. Excluded children were younger and had fewer emergency room visits for asthma than those with complete data. The authors suggested that the latter subjects had more severe asthma than the general community population of low-income children with asthma. Emergency room visits and hospitalizations for asthma were assessed by reviewing hospital records. Passive smoking by the child was measured by asking one parent if he or she or anyone else in the house smoked. Authors did not differentiate between maternal and paternal smoking; no attempt was made to assess the degree of exposure to cigarette smoke. Eight children who were active smokers were excluded. There was a significant correlation between number of emergency room visits and cigarette smoke exposure ($p = 0.008$); the mean frequency ($\pm$ SD) of annual emergency room visits observed for children exposed to passive smoking was 3.1 ± 0.4, compared to 1.8 ± 0.3 for children from nonsmoking households. Passive smoking had no effect on either the frequency of days with asthma symptoms or on the annual frequency of hospitalizations. Results were independent of ethnicity and parental employment status. The association could have been explained by lower compliance with prescribed treatment of their children's asthma by smoking parents, but the authors found no significant differences in compliance (as assessed by an index of asthma self-management activities) between smoking and nonsmoking parents. The authors estimated that the additional cost for emergency care for asthma was \$92 $\pm$ \$68 per family per year.

250103201 3

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

O'Connor and coworkers (1987) performed bronchial challenges with subfreezing air in 292 subjects 6 to 21 years of age. They were selected from 879 eligible subjects of the same age who were participating in a longitudinal study on respiratory illnesses in East Boston. An attempt was made to include as many subjects as possible who reported a history of asthma or wheezing on standardized questionnaires. Therefore, the latter group of subjects were overrepresented among those tested. The change in FEV_1 caused by subfreezing air was significantly higher in asthmatic subjects whose mothers smoked at least 1 cigarette per day than in those whose mothers were nonsmokers. This relationship was independent of age, sex, height, personal smoking, paternal smoking, atopy, and baseline lung function. There was no relationship between maternal smoking and response to cold air among nonasthmatics.

Murray and Morrison (1989) studied 415 nonsmoking children aged 1 to 17 years consecutively referred to an allergy clinic in Vancouver, Canada, for asthma or recurrent wheezing of the chest. Questionnaires were administered to the parents of all children at the time of their first visit. Forced expiratory flows and bronchial reactivity to histamine were also measured. An asthma symptom score was calculated for each subject based on the severity of asthma and the need for medication, as reported by parents. Children of smoking mothers had significantly higher indices of asthma severity ($p < 0.01$) and significantly lower FEV_1 (84.4% predicted vs. 77.3% predicted, $p < 0.01$) than did children of nonsmoking mothers. They were also significantly more responsive to histamine than were children of nonsmoking mothers ($p = 0.01$). The effect was present in both genders but was stronger for boys than for girls. Also, the effect was stronger for older children (12 to 17 years of age) than for children aged ≤ 6 years of age. The authors also reported a positive correlation between length of exposure to ETS and asthma symptom score. It is unlikely that these results can be explained by parental overreporting because the association between passive smoking and severity of symptoms paralleled that between passive smoking and objective measurements of severity.

In their previously reviewed report (Section 5.1.1), Krzyzanowski and coworkers (1990) found that children exposed to ETS and to > 60 ppb of formaldehyde had significantly higher prevalence rates of asthma than those exposed to only one of these contaminants or to none (OR for the latter comparison = 9.0; 95% C.I. = 2.4-34.0). No such association was seen among adult household members. It is unlikely that this association is attributable to parental overreporting of asthma because the authors relied on objective measurement of indoor formaldehyde concentrations.

Sherman and collaborators (1990) reported on the results of a longitudinal study of determinants of asthma in a sample of 770 schoolchildren enrolled in East Boston in 1974.

250103201H

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Questionnaires were used to obtain data on respiratory symptoms and illnesses, cigarette smoking history of parents and children, and household demographics. They were administered on entry and for 11 consecutive years (1978-1988). Parents answered for children aged 9 or less, except for questions on the child's smoking history. The authors identified risk factors for the onset of asthma the occurrence of which antedated the time of first diagnosis of asthma. There was no significant relationship between maternal smoking and either prevalence of asthma at the first survey or incidence of new cases of asthma during follow-up (sex-adjusted RR = 1.1; 95% C.I. = 0.7-1.7). The authors considered it unlikely that this finding could be due to exposure levels too low to increase the risk of asthma. However, no effort was made to assess the relationship between incidence of asthma and number of cigarettes smoked by parents. Likewise, no effort was made to determine the possible role of factors known to modify exposure to ETS such as parental socioeconomic level (Strachan et al., 1989).

Weitzman and coworkers (1990) studied 4,331 children aged 0 to 5 years who were part of the U.S. National Health Interview Survey. Children were categorized as having asthma if their parents reported that asthma was current at the time of interview and had been present for more than 3 months. Mothers were asked about their smoking habits during and after pregnancy. Odds of having asthma were 2.1 times as high (95% C.I. = 1.3-3.3) among children of mothers who smoked ≥ 10 cigarettes per day than among children of nonsmoking mothers. The risk of having asthma was not significantly increased in children of mothers who smoked < 10 cigarettes per day. Use of asthma medication was also more frequent among children of mothers who smoked ≥ 10 cigarettes per day (OR = 4.1; 95% C.I. = 1.9-8.9). Results did not change significantly after controlling for gender, race, presence of both parents, family size, and number of rooms in the households. No information was available on parental respiratory symptoms or socioeconomic status. The results of this study could be partially explained by overreporting of asthma by smoking mothers.

Oldigs and collaborators (1991) exposed 11 asthmatic children to ETS and to ambient air for 1 hour. They found no significant difference in lung function or in bronchial responsiveness to histamine after ETS exposure when compared to sham exposure. The study was only designed to determine if acute exposures to ETS caused immediate effects and did not assess the changes induced by chronic exposure to ETS.

Martinez and coworkers (1991b) studied incidence of new cases of asthma in a population sample of 774 out of 786 eligible children aged 0 to 5 years enrolled in the Tucson study of chronic obstructive lung disease. At the time of enrollment, standardized questionnaires about personal respiratory history and cigarette smoking habits were answered by the child's parents.

25010320 15

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Surveys were performed on an approximately yearly basis, and parents were asked if the child had been seen by a doctor for asthma in the previous year. There were 89 (11.5% of the total) new cases of asthma during follow-up. Children of mothers with ≤ 12 years of formal education and who smoked ≥ 10 cigarettes per day were 2.5 times as likely (95% C.I. = 1.4-4.6) to develop asthma as were children of mothers with the same education level who did not smoke or smoked < 10 cigarettes per day. This relationship was independent of self-reported symptoms in parents. Decrements in lung function paralleled the increase in asthma incidence (see Section 7.7.1). No relationship was observed between maternal smoking and asthma incidence among children of mothers with > 12 years of formal education.

7.6.2. Summary and Discussion on Asthma

There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease. Several studies have found that bronchial responsiveness is more prevalent and more intense among asthmatic children exposed to maternal smoke. Emergency room visits are more frequent in children of smoking mothers, and these children have also been found to need more medication for their asthma than do children of nonsmoking mothers (see Table 7-4).

A simple bronchospastic effect of cigarette smoke is probably not responsible for the increased severity of symptoms associated with passive smoking because acute exposure to ETS has been found to have little immediate effect on lung function parameters and airway responsiveness in asthmatic children. Therefore, the mechanisms by which passive smoking enhances asthma in children who already have the disease are likely to be similar to those responsible for inducing asthma and entail chronic exposure to relatively high doses of ETS (see discussion below). Murray and Morrison (1988) reported that ETS exposure decreased lung function and increased medication requirements in asthmatic children only during the cold, wet season and not during the dry, hot season in Vancouver, Canada. These seasonal differences may be at least partly explained by the finding by Chilmonczyk and collaborators (1990) that urine cotinine levels of children exposed to ETS are significantly higher in winter than in summer. These seasonal fluctuations also suggest that the effects of passive smoking on asthma severity are reversible and that decreasing exposure to ETS could prevent many asthmatic attacks in affected children.

New evidence available since the Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) also indicates that passive smoke exposure increases the number of new cases of asthma among children who have not had previous episodes (see Table 7-7 for results and

2501032016

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

references). Although most studies are based on parental reports of asthma, it is highly unlikely that the relationship between asthma and ETS exposure is entirely attributable to reporting bias. In fact, concordance in the relationship between ETS exposure and both questionnaires and objective parameters such as lung function or bronchial provocation tests has been reported in several studies. The association is also biologically plausible; the mechanisms that are likely to be involved in the relationship between ETS exposure and asthma have been extensively discussed in Section 7.2. The consistency of all the evidence leads to the conclusion that ETS is a risk factor for inducing new cases of asthma. The evidence is suggestive of a causal association, but not conclusive.

Data suggest that levels of exposure required to induce asthma in children are high; in fact, most recent and earlier studies that classified children as exposed to ETS if the mother smoked one cigarette or more usually failed to find any effect of ETS on asthma prevalence or incidence. Furthermore, two recent large studies found an increase in the prevalence (Weitzman, 1990) or incidence (Martinez et al., 1991b) of asthma only if the mother smoked 10 cigarettes per day or more. It is also important to consider that, for any level of parental smoking, exposure to ETS is higher in children belonging to families of a lower socioeconomic level (Strachan, 1989) and that the relationship of maternal smoking to asthma incidence may be stronger in such families (Martinez et al., 1991b). Concomitant exposure to other pollutants may also enhance the effects of ETS (Krzyzanowski, 1990).

7.7. ETS EXPOSURE AND SUDDEN INFANT DEATH SYNDROME

The relationship between ETS exposure and sudden infant death syndrome (SIDS) was not addressed in either the Surgeon General's report (U.S. DHHS, 1986) or in the NRC report (1986). Because of the importance of this syndrome as a determinant of infant mortality and because of the available evidence of an increased risk of SIDS in children of smoking mothers, the issue has been added to this report (Table 7-8).

SIDS is the most frequent cause of death in infants aged 1 month to 1 year. Approximately 2 out of every 1,000 live-born infants (more than 5,000 in the United States alone each year) die suddenly and unexpectedly, usually during sleep, and without significant evidence of fatal illness at autopsy (CDC, 1989). The cause or causes of these deaths are unknown. The most widely accepted hypotheses suggest that some form of respiratory failure is involved with most cases of SIDS.

In 1966, Steele and coworkers (1966) first reported that maternal smoking was associated with an increased incidence of SIDS. They studied the hospital records of 80 infants who had

25010320017

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

died of SIDS in Ontario, Canada, during 1960-1961 and compared them with 157 controls matched for date of birth, sex, hospital at which the child was born, and parity of the mother. Infants of mothers who smoked 1 to 19 cigarettes per day were twice as likely (OR = 2.1; 95% C.I. = 1.1-3.8) to die of SIDS as were infants of nonsmoking mothers. The odds ratio was 3.6 (95% C.I. = 1.7-7.9) when infants of mothers who smoked 20 or more cigarettes per day were compared to infants of nonsmoking mothers. The authors reported that the risk of dying of SIDS was higher in low-birthweight infants whose mothers smoked when compared to low-birthweight infants whose mothers did not smoke. However, they made no effort to control for other confounders that were related both to maternal smoking and to SIDS, such as maternal age and socioeconomic status. In addition, they made no reference to the relative roles of in utero exposure to tobacco smoke products and postnatal ETS exposure.

Naeye and collaborators (1976) studied 59,379 infants born between 1959 and 1966 in participating hospitals from several U.S. cities. After meticulous investigation of clinical and postmortem material, they identified 125 of these infants (2.3 per 1,000 live births) as having died of SIDS and compared them with 375 infants matched for place of birth, date of delivery, gestational age, sex, race, and socioeconomic status. Infants of mothers who smoked were more than 50% more likely (OR = 1.6; 95% C.I. = 1.0-2.4) to die of SIDS than were those of mothers who denied smoking. When compared with the latter, infants of mothers who smoked 6 or more cigarettes per day were 2.6 times more likely (95% C.I. = 1.7-4.0) to die of SIDS. The authors made no attempt to distinguish between in utero exposure to tobacco smoke products and ETS exposure after birth.

Bergman and Wiesner (1976) selected 100 well-defined cases of SIDS occurring in white children in King County, Washington. These cases were matched for race, sex, and birth date with 100 controls. Questionnaires were mailed to the mothers of cases and controls, but only 56 cases and 86 controls returned them. Mothers who did not respond tended to be younger and poorer. A higher proportion of mothers of SIDS victims smoked cigarettes during pregnancy (61% vs. 42%). Infants of mothers who smoked after delivery were 2.4 times as likely (95% C.I. = 1.2-4.8) to die of SIDS as were infants of nonsmoking mothers. The relationship between postnatal exposure to ETS and SIDS was significantly stronger and only reached statistical significance for mothers aged 25 years or less (OR = 4.4; 95% C.I. = 1.7-11.2). Infants of mothers aged 25 years or less who smoked 20 or more cigarettes per day were 7.7 times as likely to die of SIDS (95% C.I. = 1.7-35.4) as were infants of nonsmoking mothers. Effects were independent of maternal education. The authors did not try to determine the independent effects of pre- and postnatal exposures to maternal smoking on the incidence of SIDS.

25010320 18

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Lewak and coworkers (1979) studied all infants who died during the first year of life and who were enrolled in a health plan in Oakland, California. Using predefined criteria, they classified 44 infants (2.3 per 1,000 live births) as having died of SIDS and compared them with the rest of the population for several possible risk factors for SIDS. Mothers of infants who died of SIDS were 4.4 times (95% C.I. = 2.1-9.2) as likely to be smokers as mothers of infants who survived. Paternal smoking had no significant influence on SIDS frequency. The authors made no effort to control for possible confounding factors, nor did they discriminate between the possible roles of prenatal and postnatal exposure to tobacco smoke products.

Malloy and coworkers (1988) linked birth and death certificates to study possible risk factors for neonatal and postneonatal mortality in over 305,000 singleton white live births in Missouri. They identified 372 infants whose deaths were attributed to SIDS (1.2 per 1,000 live births). Infants whose mothers smoked were 1.8 times as likely (95% C.I. = 1.4-2.2) to die of SIDS than were infants of nonsmoking mothers. This relationship was independent of maternal marital status, education level, age, parity, and child's birthweight. There were no data available that would have allowed one to differentiate the effects of pre- and postnatal exposure to tobacco smoke products.

Hoffman and collaborators (1988) reported on the results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome risk factors. They studied 800 SIDS cases and 1,600 control infants collected at six study centers across the United States. Control infants were matched for age only (N = 800) or for age, low birthweight, and race (N = 800). SIDS cases were 3.8 and 3.4 times as likely to have smoking mothers as the first and second control groups mentioned earlier, respectively ($p < 0.005$ for both comparisons). There were no data on pre- and postnatal exposure to tobacco smoke products.

Haglund and Cnattingius (1990) examined risk factors for SIDS in a prospective study based on more than 279,000 Swedish infants who survived the first week of life. SIDS was reported as the sole cause of death in 190 infants (0.7 per 1,000), and in most cases the diagnosis was confirmed by the results of an autopsy. Infants of mothers who smoked 1 to 9 cigarettes per day were 1.8 times as likely (95% C.I. = 1.2-2.6) to die of SIDS as were infants of nonsmoking mothers. Infants of mothers who were heavy smokers had an even higher risk (OR = 2.7; 95% C.I. = 1.9-3.9) of dying of SIDS, suggesting an exposure-response relationship. These findings were independent of birthweight, maternal age, social situation, parity, sex, and type of birth. No information was available regarding smoking in the household by either mother or father after the infant's birth.

250103201

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Mitchell and coworkers (1991) studied SIDS cases occurring in several health districts in New Zealand between 1 November 1987 and 31 October 1988. After careful assessment of the material available from necropsy, 162 infants were classified as having died of SIDS (3.6 per 1,000 live births). These cases were matched for age with three to four times as many controls. The researchers interviewed the parents of and obtained complete information for 128 cases and 503 controls. Information on maternal smoking during pregnancy (as a yes/no variable) was obtained from the obstetric records, whereas information on number of cigarettes smoked by the mother in the 2 weeks preceding the interview was obtained from questionnaires. Mothers of infants who died of SIDS were 3.3 times as likely (95% C.I. = 2.2-5.0) to smoke during pregnancy as were mothers of controls. The analysis of the relationship between maternal smoking after the child's birth and frequency of SIDS showed clear evidence of a biological gradient of risk. Odds ratios were as follows: 1.9 (95% C.I. = 1.0-3.5) for mothers who smoked 1 to 9 cigarettes per day; 2.6 (95% C.I. = 1.5-4.7) for mothers who smoked 10 to 19 cigarettes per day; and 5.1 (95% C.I. = 2.9-9.0) for mothers who smoked 20 or more cigarettes per day. The association between maternal smoking and SIDS frequency was independent of antenatal care, maternal age, maternal education, marital status, sex, neonatal problems, parity, socioeconomic status, birthweight, gestational age, race, season of death, sleep position at death, and breastfeeding.

In summary, there is strong evidence that infants whose mothers smoke are at increased risk of dying suddenly and unexpectedly during the first year of life. This relationship is independent of all other known risk factors for SIDS, including low birthweight and low gestational age. The finding that there is a biological gradient of risk extending from nonsmoking mothers to those smoking more than 20 cigarettes per day adds to the evidence that exposure to cigarette smoke products is involved in the sequence of events that result in SIDS.

Available studies cannot differentiate the possible effects with respect to SIDS of exposure to tobacco smoke products in utero from those related to passive smoking after birth. As explained earlier (Section 7.2.2), both human and animal studies show that maternal smoking during pregnancy may modify and potentiate the effects of postnatal ETS exposure. The relationship between maternal smoking and SIDS is independent of low birthweight, which is the most important known effect of maternal smoking during pregnancy. In addition, the incidence of SIDS is apparently associated with days of higher air pollution levels (Hoppenbrouwers, 1981), which could indicate a direct effect of airborne contaminants.

In view of the fact that the cause of SIDS is still unknown, it is not possible to assess the biological plausibility of the increased incidence of SIDS related to exposure to ETS.

250102020

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Consequently, at this time this report is unable to assert whether or not passive smoking is a risk factor for SIDS.

7.8. PASSIVE SMOKING AND LUNG FUNCTION IN CHILDREN

The Surgeon General's report (U.S. DHHS, 1986) reviewed 18 cross-sectional and longitudinal studies on the effects of ETS exposure on lung function in children (Table 7-9). The report concluded that "the available data demonstrate that maternal smoking reduces lung function in young children" (page 54). The hypothesis was proposed that passive smoking during childhood, by affecting the maximal level of lung function attainable during early adult life, may increase the subsequent rate of decline of lung function and, thus, increase the risk of chronic obstructive lung disease.

The NRC report (1986) reached similar conclusions after reviewing 12 articles (Table 7-9). The authors' summary asserted that "estimates of the magnitude of the effect of parental smoking on FEV_1 function in children range from 0 to 0.5% decrease per year. This small effect is unlikely by itself to be clinically significant. However, it may reflect pathophysiologic effects of exposure to ETS in the lungs of the growing child and, as such, may be a factor in the development of chronic airflow obstruction in later life" (page 215).

7.8.1. Recent Studies on Passive Smoking and Lung Function in Children

Studies appearing since the 1986 reports are presented in Table 7-10.

Lung function measurements were included in the cross-sectional study by O'Connor and collaborators (1987) described earlier (Section 7.6.1). When compared to 97 nonasthmatic children of nonsmoking mothers (mean age ± SEM = 12.8 ± 0.3 years), 168 nonasthmatic children of smoking mothers (mean age ± SEM = 12.9 ± 0.2 years) had significantly lower mean percentage of predicted FEV_1 (mean ± SEM = 108.0 ± 1.4 vs. 101.4 ± 1.1, respectively, $p < 0.001$) and significantly lower FEF_{25-75} (103.0 ± 2.3 vs. 88.2 ± 1.5, respectively, $p < 0.001$). These effects were independent of personal smoking by the child.

Lebowitz and coworkers (1987) reported on the results of a longitudinal study of pulmonary function development in Tucson, Arizona. The authors analyzed 1,511 observations over an average follow-up period of 8.8 years in 353 subjects aged 5.5 to 25 years. The last available lung function value (as residuals after regressing the data with different power functions of age and height) was used as outcome. Residuals for vital capacity were significantly higher among subjects aged 14 years or less at entry whose mothers smoked cigarettes (mean = +3.3 vs. -1.4 among nonexposed subjects, $p < 0.001$). Parental smoking had no direct effect on outcome

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

FEV_1 or $V_{max}50\%$, but showed significant interactions with personal smoking and parental history of airway obstructive diseases in their effects on $V_{max}50\%$; subjects who had started smoking or whose parents had airway obstructive diseases and were exposed to ETS had the lowest $V_{max}50\%$ residuals at the end of follow-up.

In subsequent reports, Lebowitz and Holberg (1988) and Tager and coworkers (1987) reanalyzed two sets of longitudinal pulmonary function data: the one on which the preceding study from Tucson, Arizona, was based (Lebowitz, 1987) and data for children of similar age from East Boston, Massachusetts (Tager, 1983). The objective was to determine if the different answers in regard to the effect of maternal smoking (significant for the Boston study; no effect for the Tucson study) were due to the use of different statistical tools. Applying the same multivariable analysis of covariance for both data sets, Lebowitz and Holberg (1988) confirmed the positive effect of maternal smoking of $FEF_{25-75\%}$ with the data from Boston ($p < 0.05$) and the lack of a significant effect of maternal smoking on $V_{max}50\%$ with the data from Tucson, Arizona. A first-order autoregressive model applied by Tager and collaborators (1987) to both data sets showed effects of maternal smoking on FEV_1 with the Boston data but not with the Tucson data. The authors concluded that the most likely factor responsible for the disparate results was the exposure difference in the two populations.

Tsimoyianis and collaborators (1987) compared the prevalence of low levels of $FEF_{25-75\%}$ (< 70% of predicted) in athletes exposed and unexposed to ETS (for more information on this study see Section 7.4.1). Eighteen out of 132 exposed athletes (13.6%) had low $FEF_{25-75\%}$ compared with 2 out of 61 (3.3%) unexposed athletes (OR = 4.7; 95% C.I.= 1.1-20.8).

Kauffmann and collaborators (1989b) assessed familial factors related to lung function in a cross-sectional study of 1,160 French children. Levels of lung function (FEV_1 and $FEF_{25-75\%}$) were significantly lower in children with mothers who smoked when compared to those whose mothers were nonsmokers. The authors reported a loss of 10 mL of FEV_1 ($p < 0.05$) and of 15 mL/s of $FEF_{25-75\%}$ ($p < 0.01$) for every gram of tobacco smoked per day by the mother. These associations were independent of sex, town of origin, age, height, weight, and intrafamilial aggregation of lung function. There was no effect of paternal smoking on lung function.

Chan and coworkers (1989) performed lung function tests in a cohort of 130 children of low birthweight (under 2,000 grams) at 7 years. These authors had previously reported on the respiratory outcome of these same children (see Section 7.5.1). Children of low birthweight whose mothers smoked had significantly lower values of percentage of predicted $V_{max}75\%$ than did low-birthweight children whose mothers did not smoke (80.7% vs. 91.4%, $p < 0.01$). This association was independent of sex, birthweight, neonatal respiratory illness, and treatment. As 92% and 79%

25010202

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

of mothers who smoked when the child was 7 years old were smokers before and during their pregnancy, respectively, it was not possible to determine whether the effect of maternal smoking was fetal or postnatal.

The study by Dijkstra and collaborators (1990) has been described earlier (Section 7.5.1). Together with respiratory symptoms, the authors studied lung function and its relationship with indoor exposures to ETS and nitrogen dioxide in a population of 634 Dutch children 6 to 12 years of age. When compared to unexposed children, children exposed to ETS had significantly lower levels of FEV_1 (—1.8%; 95% C.I. = —0.2 to —3.3), $FEF_{25-75\%}$ (—5.2%; 95% C.I. = —1.4 to —8.8) and Peak Flow (—2.8%; 95% C.I. = —0.6 to —4.8). Adjustment for smoking by the mother when she was pregnant with the investigated child removed little of the effect of current ETS exposure on lung function. The authors suggested that this indicated that the associations seen at ages 6 to 12 years were not just mirroring harm that was caused when the children were exposed in utero to tobacco smoke components inhaled by the mother. There was no association between exposure to NO_2 and lung function.

A previously mentioned study by Strachan and coworkers (1990) (Section 7.5.1) included lung function measurements in 757 children. Lung function variables were adjusted for sex, height, and housing characteristics. The authors found a significant negative correlation between salivary cotinine concentrations and levels of $FEF_{25-75\%}$ ($p < 0.05$) and $V_{max}75\%$ ($p < 0.05$). For these indices, the difference between adjusted mean values for the top and bottom quintiles of salivary cotinine was of the order of 7% of the mean value in the children with undetectable levels.

The longitudinal study by Martinez and coworkers (1991b) has been reviewed earlier (Section 7.6.1). In addition to their findings on incidence of childhood asthma, these authors reported that, at the end of follow-up, children of mothers with ≤ 12 years of formal education and who smoked ≥ 10 cigarettes per day had 15% lower mean values for percentage of predicted $FEF_{25-75\%}$ than did children of mothers of the same level of education who were nonsmokers or smoked < 10 cigarettes per day. Maternal smoking had no effect on percentage of predicted $FEF_{25-75\%}$ values in children of mothers who had at least some education beyond high school. Female children of smoking mothers (≥ 10 cigarettes) had 7% higher Vital Capacity than did female children of mothers who were nonsmokers or light smokers (< 10 cigarettes/day), and this was independent of maternal education. All differences were still significant after controlling for parental history of respiratory disease.

05/15/92
25010320 23

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

7.8.2. Summary and Discussion on Pulmonary Function in Children

This report concludes that there is a causal relationship between ETS exposure and reductions in airflow parameters of lung function (FEV_1, $FEF_{25-75\%}$, $V_{max}50\%$, or $V_{max}75\%$) in children. For the population as a whole, these reductions are small relative to the intraindividual variability of each lung function parameter; for $FEF_{25-75\%}$, for example, reductions range from 3% to 7% of the levels seen in unexposed children, depending on the study analyzed. Groups of particularly susceptible or heavily exposed subjects have larger decrements: Exposed children of low birthweight, for example, had 12% lower $V_{max}75\%$ than did children of similar birthweight who were not exposed to ETS (Chen, 1989). Likewise, children of less educated mothers who smoked > 10 cigarettes per day were shown to have 15% lower mean $FEF_{25-75\%}$ than children of less educated mothers who did not smoke or smoked < 10 cigarettes per day. This stronger effect may be explained by Strachan and coworkers' (1989) finding that children of lower socioeconomic status have higher salivary cotinine levels, for any amount of parental smoking, than do children of higher socioeconomic status.

The studies reviewed suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. In fact, exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

New longitudinal studies have demonstrated that young adults who were exposed earlier in life to ETS are also more susceptible to the effects of active smoking (Lebowitz et al., 1987). In addition, Sherrill and collaborators (1990) showed, in a longitudinal study, that children who entered a longitudinal study with lower levels of lung function still had significantly lower levels later in life. The high degree of tracking shown by these spirometric parameters implies that the decrements in lung function related to passive smoking may persist into adulthood. Although the subsequent rates of decline in lung function of these subjects has yet to be studied in detail, the findings by Sherrill and coworkers (1990) support the idea proposed by the Surgeon General's report (U.S. DHHS, 1986) that, by the mechanisms described above, passive smoking may increase the risk of chronic airflow limitation.

7.9. PASSIVE SMOKING AND RESPIRATORY SYMPTOMS AND LUNG FUNCTION IN ADULTS

Both the NRC report (1986) and the Surgeon General's report extensively reviewed the evidence then available on involuntary smoking and respiratory health in adults. The Surgeon

25010320 24

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

General's report concluded that healthy adults exposed to ETS may have small changes on pulmonary function testing but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to ETS alone. The report added that the small magnitude of the effect implied that a previously healthy individual would not develop chronic lung disease solely on the basis of ETS exposure in adult life. It was suggested that small changes in lung function may be markers of an irritant response, possibly transient, to the irritants known to be present in ETS.

The NRC report concluded that it was difficult to document the extent to which a single type of exposure like ETS affects lung function. The report attributed this difficulty to the large number of factors, including other exposures, that affect lung function over a lifetime. The report added that results in adults should be evaluated for possible misclassification of exsmokers or occasional smokers as nonsmokers, as well as possible confounding by occupational exposures to other pollutants. The authors of the report considered it "unlikely that exposure to ETS can cause much emphysema" (page 212), but that, "as one of many pulmonary insults, ETS may add to the total burden of environmental factors that become sufficient to cause chronic airway or parenchymal disease" (page 212).

7.9.1. Recent Studies on Passive Smoking and Adult Respiratory Symptoms and Lung Function

Six recent studies of respiratory symptoms and lung function in adults are presented in Table 7-11.

Svendsen and collaborators (1987) studied longitudinal data from 1,245 married American men aged 35 to 57 years who reported that they had never smoked. Subjects who had smoking wives had significantly higher mean levels of exhaled carbon monoxide (7.7 vs. 7.1 ppm, $p < 0.001$) but not of serum thiocyanate. These men also had lower levels of age- and height-adjusted FEV_1 (mean difference = 99 ml; 95% C.I. = 5 ml-192.4 ml). However, those with wives who smoked 20 or more cigarettes per day had higher mean adjusted FEV_1 (3,549 ml) than those with wives who smoked 1 to 19 cigarettes per day (3,412 ml), whereas nonexposed subjects had mean adjusted FEV_1 of 3,592 ml.

Kalandidi and coworkers (1987) studied 103 Greek ever-married women aged 40 to 79 who were admitted in 1982 and 1983 to a hospital in Athens with obstructive or mixed type reduction of pulmonary function, without improvement after bronchodilatation. The women denied that they had ever been smokers, and their husband's smoking habits were compared with those of 179 ever-married controls of the same age selected from visitors to the hospital. Patients were 1.9 times more likely to have smoking spouses than were controls (95% C.I. = 1.0-4.0).

25010320 25

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

However, odds ratios were higher for women whose spouses smoked 20 or fewer cigarettes per day (2.5) than for those whose spouses smoked more than 20 cigarettes per day. The unusually high number of nonsmoking women hospitalized with chronic lung disease in a 2-year period suggests that some could have severe asthma unresponsive to bronchodilators and that the results could in part illustrate exacerbation of symptoms in asthmatic women exposed to ETS.

Masi and coworkers (1988) mailed questionnaires to 818 subjects aged 15 to 35 who had previously performed detailed lung function testing and carboxyhemoglobin (COHb) measurements. A total of 636 subjects responded to the questionnaire and 293 denied having smoked regularly before the date of the lung function tests. All but five subjects had COHb values below 5 grams %. Questionnaires assessed past and present ETS exposure, both at home and at work. Indices of cumulative exposure to ETS at home and at work were calculated from the number of reported smokers on each location, the smoking conditions reported for each area, and the number of years of exposure. In men, there were significant inverse relationships between cumulative exposure to ETS in the home and maximal expiratory flows at low lung volumes. A more detailed analysis showed that in these subjects, exposure before 17 years of age had the strongest effects on lung function, whereas exposure in the 5 years preceding the lung function tests had no effect on lung function. Exposure at work significantly decreased the diffusing characteristics of the lung in women.

Kauffmann and collaborators (1989a) compared the results obtained from a parallel analysis of the association of passive smoking with respiratory symptoms and lung function in 2,220 American women aged 25 to 69 years and 3,855 French women aged 25 to 59 years. Women were classified according to their personal and current spouse's smoking habits. After adjusting for age, city of origin, educational level, and occupational exposure, ever-passive-smokers (excluding active smokers) had significantly more wheeze than true never-smokers (i.e., never active and with nonsmoking spouse) in the U.S. sample (OR of approximately 1.3; C.I. cannot be calculated). There was a positive trend for French passive smokers to have more chronic cough (OR = 1.4) and dyspnea (OR = 1.2), but both results could be due to chance (95% C.I. = 0.8-2.4 and 0.9-1.6, respectively). In both samples, no significant decrease of lung function was observed for passive smokers compared to true never-smokers in the whole sample, although FEV_1/FVC values for ever-passive-smokers tended to be intermediate between those of true never-smokers and ex-smokers or active smokers. French women aged 40 or older who were passive smokers had significantly lower FVC ($p < 0.01$) and FEV_1 ($p < 0.01$) than did true never-smokers, but no such effect was seen among American women of the same age.

250103202G

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Hole and coworkers (1989) studied cardiorespiratory symptoms and mortality in a cohort of 7,997 subjects aged 45 to 64 and followed for 11 years in urban west Scotland. A self-administered questionnaire was used in 1972-76 to assess respiratory symptoms and active smoking by each member of the household. When compared to true never-smokers (i.e., persons who were not active smokers and did not live with an active smoker), passive smokers were invariably at a higher risk of having each cardiorespiratory symptom examined (including infected sputum, persistent sputum, and dyspnea), but all 95% confidence intervals for odds ratios included 1. FEV_1 (adjusted for sex, age, and height) was significantly higher in true never-smokers than in passive smokers ($p < 0.01$), but this effect was mainly due to the low adjusted FEV_1 of passive smokers with high exposure (i.e., exposed to a cohabitee who smoked > 15 cig./day; mean = 1.83 L) when compared to those with low exposure (mean = 1.89 L) or with no exposure (mean = 1.88 L). This study was initiated when there was little concern for the possible ill effects of passive smoking and is based on self-reports of active smoking by cohabitees. It is thus probably not affected by classification bias due to overreporting of symptoms by smokers.

Schwartz and Zeger (1990) studied data from a cohort of approximately 100 student nurses in Los Angeles who kept diaries of acute respiratory symptoms (cough, phlegm, chest discomfort) and for whom data on exposure to passive smoking and air pollution were available. After controlling for personal smoking, a smoking roommate increased the risk of an episode of phlegm (OR = 1.4; 95% C.I. = 1.1-1.9) but not of cough. The authors also excluded asthmatics (on the assumption that medication could bias the results) and found that in this case, the odds ratio of having phlegm increased to 1.8 (95% C.I. = 1.3-2.3). The greater sensitivity of diaries of acute symptoms such as those used herein, compared with the indices of period prevalence of symptoms used in other studies, may have increased the power of this study. However, overreporting by exposed subjects is still a possible source of bias in a study that is solely based on self-report of symptoms.

7.9.2. Summary and Discussion on Respiratory Symptoms and Lung Function in Adults

Recent studies have confirmed the conclusion by the Surgeon General's report (U.S. DHHS, 1986) that adult nonsmokers exposed to ETS may have small reductions in lung function (approximately 2.5% lower mean FEV_1 in the studies by Svendsen et al. [1987] and Hole et al. [1989]). Using modern statistical tools designed for longitudinal studies, new evidence has also emerged suggesting that exposure to ETS may increase the frequency of respiratory symptoms in adults. These latter effects are estimated to be 30% to 60% higher in ETS-exposed nonsmokers compared to unexposed nonsmokers.

05/15/92

2501032027

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Because active smoking causes significant reductions in lung function and significant increases in prevalence of respiratory symptoms (U.S. DHHS, 1984), the reported effects of passive smoking in adults are biologically plausible. From a quantitative point of view, effects of passive smoking on lung function are approximately comparable to those reported for light (< 10 cig./day), male active smokers (Camilli et al., 1987). However, because of the self-selection of smokers and other factors, it is difficult to make direct quantitative comparisons between the effects of active and passive smoking. The process of self-selection is likely to occur among smokers by which more susceptible individuals never start smoking or quit smoking early in life (the "healthy smoker" effect). Therefore, lower lifetime doses may be required to elicit effects among nonsmokers than among smokers. The different nature of ETS and MS has also been discussed in previous chapters and has to be taken into account when comparing effects of active and passive smoking.

Several sources of bias and confounding factors need to be considered in studies of the effects of single exposures in adults. Classification bias due to underreporting of active smoking or past smoking may significantly affect the results of these studies. Because there is marital aggregation of smoking (i.e., smokers tend to marry smokers, and nonsmokers are more prone to marry nonsmokers), this source of misclassification is more probable among spouses of smokers and may introduce differential biases in some studies. The resulting small overestimation of effect may be nevertheless substantial for effects that are particularly subtle, such as those described for ETS exposure in adults. In addition, recent public concern with passive smoking may increase the awareness of respiratory symptoms in exposed subjects, who may be thus more prone to report symptoms than are unexposed subjects. Studies using objective measures of lung function are obviously not affected by the latter type of bias.

Adults are exposed to multiple sources of potentially harmful substances during their lifetimes, and it is not always possible to control for their effects, because often they are unknown or are unmeasurable. In general, the majority of these exposures should introduce nondifferential error to the studies, which would thus underestimate true effects. For example, a significant nondifferential error may be introduced by ETS exposure during childhood, which is known to cause decrements in lung function (see Section 7.7). Conversely, effects of ETS would be overestimated if a certain noxious exposure were more likely to occur among ETS-exposed subjects. In this sense, social factors need to be accurately controlled, because prevalence of smoking is significantly higher among less educated than among higher educated subjects (Pierce et al., 1989). Most reviewed studies have controlled for indices of socioeconomic level in a satisfactory manner. Finally, lifestyles may differ between spouses of smokers and those of

2501032028

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

nonsmokers, but it is not possible to determine a priori the effect of this confounder on the relationship between passive smoking and respiratory health.

The influence of these factors and sources of bias, together with the subtlety of the effects, may explain the inconsistent and sometimes contradictory results of the studies reviewed in this report. In fact, such variability should be expected, particularly for studies with relatively low power (i.e., low probability of finding a statistically significant difference when a difference really exists). The lack of a dose-response relationship in some studies may also be explained by the multiplicity of uncontrolled factors that may affect lung function.

In summary, recent evidence suggests that passive smoking has subtle but statistically significant effects on the respiratory health of nonsmoking adults.

2501032029

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 7-1. Studies on respiratory illness referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Surgeon General	NRC
Cameron, 1969	158	Children (6-9)	X	
Colley, 1971	2,205	Infants	X	
Colley, 1974	1,598	Children (6-14)		X
Dutau et al., 1981	892	Infants/children (0-6)		X
Fergusson et al., 1981	1,265	Infants	X	X
Leeder et al., 1976	2,149	Infants	X	X
Pedreira, 1985	1,144	Infants	X	X
Pullan and Hey, 1982	130	Children (10-11)	X	
Rantakallio, 1978	3,644	Infants/children (0-5)	X	X
Speizer et al., 1980	8,120	Children (6-10)	X	X
Ware et al., 1984	8,528	Children (5-9)	X	

25010320

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-2. Recent epidemiologic studies of effects of passive smoking on acute lower respiratory tract illnesses (LRIs)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Breese Hall et al. (1984)	Cases: 29 infants hospitalized with bronchiolitis due to respiratory syncytial virus (RSV) Controls: 58 infants hospitalized for nonrespiratory conditions; 58 infants hospitalized due to LRIs not due to RSV	Parental questionnaire	See population studied	Cases vs. controls OR = 4.8 (1.8-13.0) (>5 cig./day vs. none) LRI controls vs. non-LRI controls OR = 2.7 (1.3-5.7)	Cases matched to controls for age, sex, race, month of admission, form of payment. Selection bias not ruled out
Chen et al. (1986)	1,058 infants born in Shanghai, China	Parental self-administered questionnaire; number cigarettes smoked by household members	Admissions to hospital for respiratory illness as reported by parents	Cig./day OR 1-9 1.2 (0.6-2.3) >9 1.9 (1.1-3.4)	Controlling for: crowding, paternal education, feeding practice, birthweight, family history of chronic respiratory illness

DRAFT--DO NOT QUOTE OR CITE

250103203 1
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Chen et al. (1988)	2,227 infants born in Shanghai, China	Household self-administered questionnaire	Incidence of hospitalization for respiratory illness, incidence of bronchitis/pneumo-nia first 18 mo. of life	First 6 mo. of life: OR = 3.0 (1.6-5.7); 7-18 mo. of life: OR = 1.8 (1.0-3.2)	No smoking mothers. Controlling for sex, birth-weight, feeding practices, nursery care, paternal education, use of coal for cooking, family history of chronic respiratory illness
Chen (1989)	Same as above	Same as above	Same as above	First 18 mo. of life: Incidence density ratio (IDR) = 1.6 for breast-fed babies; IDR = 3.4 for non-breast-fed babies; confidence intervals not calculable	

DRAFT--DO NOT QUOTE OR CITE

05/15/92
250103203Z

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
McConnochie and Roghmann (1986a)	53 infants with bronchiolitis; 106 controls	Parental questionnaire at mean age 8 yr.	See population studied	Cases vs. controls OR = 2.4 (1.2-4.8) (smoking mother vs. nonsmoking mother)	Cases matched to controls for sex and age. Controlling for family history of asthma, social status, older siblings, crowding. Selection bias not ruled out
Ogston et al. (1987)	1,565 infants in New Zealand	Maternal and paternal smoking habits during pregnancy by questionnaire	Upper and lower respiratory illnesses during first year of life	Paternal smoking OR = 1.43 (1.05-1.96); maternal smoking OR = 1.82 (1.25-3.64)	Upper and lower respiratory illnesses not distinguished; controlling for maternal age, feeding practices, heating type, social class

DRAFT--DO NOT QUOTE OR CITE

250103203 3
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Anderson (1988)	102 children hospitalized in Atlanta, GA, <2 yr.; 199 controls	Self-reported smoking habits of family members	LRI	No effect of parental smoking after controlling for other risk factors	Selection bias possible
Woodward et al. (1990)	2,125 children aged 18 mo. to 3 yr.	Self-administered mailed questionnaire	"Respiratory score" regarding 13 different symptoms. Top 20% compared with low 20%	OR = 2.0 (1.3-3.4) of having a smoking mother for high scores compared to low scores. No effect of paternal smoking	Controlling for parental history of respiratory illness, child care, parental occupation, maternal stress

DRAFT--DO NOT QUOTE OR CITE

250103203H

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Wright et al. (1991)	847 white children born in Tucson, AZ	Self-administered questionnaire and cotinine levels in a subsample	LRIs as assessed by the infants' pediatrician	OR = 1.5 (1.1-2.2) of having smoking mother. No effect of paternal smoking	Effects significant only for LRIs occurring in the first 6 mo. of life. Controlling for day care, room sharing, parental history of respiratory illnesses, feeding practices, sex, and maternal education

[a]95% confidence intervals in parentheses.

DRAFT--DO NOT QUOTE OR CITE

250103203S
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 7-3. Studies on middle ear diseases referenced in the Surgeon General's report of 1986

Study	No. of subjects	Age of subjects (years)
Said et al., 1978	3,290	10-20
Iversen et al., 1985	337	0-7
Kraemer et al., 1983	76	Young children (unspecified age)
Black, 1985	450	4-9
Pukander et al., 1985	264	2-3

250103203

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-4. Recent epidemiologic studies of effects of passive smoking on acute and chronic middle ear diseases

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Willatt (1986)	93 children aged 2-15 yr. admitted to hospital for tonsillectomy; 61 age- and sex-matched controls	Questionnaire answered by parents	Tonsillectomy	OR = 2.1 (1.1-4.0) of having smoking mothers	Controlling for birthweight, sex, age, feeding practices, social class, crowding, sore throats in other household members
Fleming et al. (1987)	575 children <5 yr.	Questionnaire answered by child's guardian	Upper respiratory illnesses (URI) and infections in previous 2 weeks	OR = 1.7 for URI when mother smoked. No effect on ear infection	Controlling for feeding practices, income, crowding, day care, siblings, sex, race
Tainio et al. (1988)	198 Finnish newborns followed from birth to age 2.3 yr.	Questionnaire to parents	Recurrent otitis media as diagnosed by pediatricians	No effects	No distinction between maternal and paternal smoking. Small sample

DRAFT--DO NOT QUOTE OR CITE

05/15/92 250103203?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Reed and Lutz (1988)	24 cases of acute otitis media; 25 controls	Questionnaire to parents	Abnormal tympanometry	OR = 4.9 (1.4-17.2) of having smokers at home	Small sample; selection bias cannot be ruled out
Hinton (1989)	115 children aged 1-12 yr. admitted for grommet insertion; 36 controls aged 2-11 yr. Great Britain	Questionnaire to parents	Being admitted for grommet insertion	OR = 2.1 (1.0-4.5) of having smoking parents	No control for confounders; selection bias not ruled out
Teele et al. (1989)	877 children observed for 1 yr.; 698 observed for 3 yr.; 498 observed for 7 yr. in Boston	Questionnaire to parents	Acute otitis media. Number of days with middle ear effusion	13% more acute otitis during 1st yr. of life. More days with middle ear effusion ($p<0.009$) only during 1st yr. No effects after controlling for confounders.	No distinction between paternal and maternal smoking; parents smoking 1 cig./day included among smokers.
Corbo et al. (1989)	1615 children aged 6-13 yr. in Abruzzo, Italy	Parental questionnaire	Child's snoring as reported by parents	OR = 1.8 (1.1-3.0) for moderate smokers (1-19 cig./day) OR = 1.9 (1.2-3.1) for heavy smokers (≥20 cig./day)	No distinction between maternal and paternal smoking

DRAFT--DO NOT QUOTE OR CITE

05/15/92

250103203B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Strachan et al. (1989)	736 children in 3rd elementary class in Edinburgh, Scotland	Salivary cotinine level	Prevalence of middle ear effusion as assessed by tympanogram	OR for doubling salivary cotinine = 1.14 (1.03-1.27)	1/3 of cases of middle ear effusion attributable to passive smoking. Controlling for sex, housing tenure, social class, crowding, gas cooking, damp walls
Takasaka (1990)	77 children aged 4-8 yr. with otitis media with effusion; 134 controls matched for age, sex; in Sendai, Japan	Parental questionnaire	See population studied	No effect	Low power

[a]95% confidence intervals in parentheses.

DRAFT--DO NOT QUOTE OR CITE

250103203 9
5/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 7-5. Studies on chronic respiratory symptoms referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Respiratory symptoms	Surgeon General	NRC
Bland et al., 1978	3,105	Children/adol. (12-13)	Cough	X	X
Charlton, 1984	15,000	Children/adol. (8-19)	Cough	X	
Colley et al., 1974	2,426	Children (6-14)	Cough	X	X
Dodge, 1982	628	Children (8-10)	Wheeze, phlegm, cough	X	X
Ekwo et al., 1983	1,355	Children (6-12)	Cough, wheeze	X	
Kasuga et al., 1979	1,937	Children (6-11)	Wheeze, asthma	X	
Lebowitz and Burrows, 1976	1,525	Children (<15)	Cough, phlegm, wheeze	X	X
Schenker et al., 1983	4,071	Children (5-14)	Cough, phlegm, wheeze	X	X
Schilling et al., 1977	816	Children/adol. (7-16)	Cough, phlegm, wheeze	X	X
Tager et al., 1979	444	Children/adol. (5-19)	Cough, wheeze		X
Ware et al., 1984	10,106	Children (6-13)	Cough, wheeze, phlegm		X
Weiss et al., 1980	650	Children (5-9)	Cough, phlegm, wheeze	X	X

25010320 40 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-6. Recent epidemiologic studies of effects of passive smoking on cough, phlegm, and wheezing

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
McConnochie and Roghman (1986b)	223 children aged 6-10 yr. in Rochester, NY	Parental questionnaire	Wheezing in the previous 2 yr.	OR = 2.2 (1.0-4.8) for maternal smoking. No effect of paternal smoking	Effect disappeared after controlling for confounders. Strong interaction between smoking and family history of allergy (OR = 4.5 [1.7-12.0])
Park and Kim (1986)	3,651 children aged 0-14 yr. in South Korea	Questionnaire to household members	Cough in the 3 mo. prior to interview	OR = 2.4 (1.4-4.3) for families smoking 1-14 cig./day; OR = 3.2 (1.9-5.5) for families smoking ≥15 cig./day	Results only significant among families whose adult members did not have chronic cough

DRAFT--DO NOT QUOTE OR CITE

05/15/92
250103204

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Bisgaard et al. (1987)	5,953 infants enrolled at birth in Denmark	Maternal questionnaire	Episodes of wheeze during 1st yr. of life	OR = 2.7 (1.8-4.0) for children whose mothers smoked ≥3 cig./day	Controlling for social status and sex. Almost ⅛ of original sample did not participate in the study
Geller-Bernstein et al. (1987)	80 children aged 6-24 mo. in Israel	Parental questionnaire	Persistent wheeze as assessed by physician after 1½ yr. of follow-up	OR = 3.1 (1.1-8.9) of having smoking parents	No control for parental symptoms
Cogswell et al. (1987)	100 infants of allergic parents enrolled at birth. 73 still followed at age 5 yr.	Parental questionnaire	Number of subjects who developed wheezing at different times after birth	By 5 yr., 63% of parents who smoked had wheezing children, compared with 37% of nonsmoking parents ($p<0.05$)	>1/4 of subjects lost to follow-up
Toyoshima et al. (1987)	48 wheezy children <3 yr. followed in Osaka, Japan	Parental questionnaire	Number of children still wheezing at end of follow-up	OR = 11.8 (1.3-105.0) for children living in smoking households	Selection bias cannot be ruled out
Tsimoyianis et al. (1987)	193 12 to 17 year-old high school athletes	Questionnaire to the child on household smoking habits	Self-report of cough, bronchitis, wheeze, and shortness of breath	No effect on bronchitis, wheeze, shortness of breath. Increased frequency of cough ($p=0.08$)	Reporting bias cannot be ruled out

DRAFT--DO NOT QUOTE OR CITE

05/15/92

25010320H2

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results*	Observations
Andrae et al. (1988)	4,990 children aged 6 mo. - 16 yr. in Norrkoping, Sweden	Self-report of smoking by parents	Exercise-induced cough as reported by parents	OR = 1.4 (1.1-1.8) for children whose parents smoked	No effort made to control for active smoking in older children
Somerville et al. (1988)	7,144 children aged 5-11 yr. in England and Scotland; 134 controls matched for age, sex in Sendai, Japan	Questionnaire answered by child's mother	Parental reports of respiratory symptoms in the child	Among English children whose parents smoked ≥20 cig./day OR = 1.6 (1.2-2.2) of having "wheezy chest most nights"	
Rylander et al. (1988)	67 children aged 4-7 yr. hospitalized with respiratory syncytial virus bronchiolitis in Stockholm, Sweden	Parental questionnaire	Subsequent occasional and recurrent wheezing	Occasional wheezing OR = 4.3 (1.1-16.4) in children in smoking parents. No effect on recurrent wheezing	Small number of subjects
Strachan (1988)	1,012 schoolchildren 6.5-7.5 yr. old in Edinburgh, Scotland	Parental questionnaire	Respiratory symptoms in children	No effect on wheeze. Cough at night, OR = 1.6 (1.1-2.6) in children living with one smoker; OR = 2.5 in children living with two smokers	

DRAFT--DO NOT QUOTE OR CITE

250103204

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Lewis et al. (1989)	60 cases of chronic cough aged <6 yr.; 60 controls; in Salford, United Kingdom	Parental questionnaire	See population studied	OR = 1.7 (0.8-3.5) in children living with a smoker	Low power
Neuspiel et al. (1989)	9,670 children enrolled at birth in Great Britain	Parental questionnaire at birth, at age 5 yr. and at age 10 yr.	Wheeze between ages 1 and 10 yr.	Cumulative incidence: 5.2% mother non-smoker, 6.6% mother smoked 1-4 cig./day, 7.5% mother smoked 5-11 cig./day, 8.1% mother smoked 15-24 cig./day, 8.9% mother smoked >24 cig./day	Independent of sex, allergy, smoking during pregnancy, paternal smoking, crowding, dampness, feeding practices, gas cooking, social status, maternal respiratory symptoms

DRAFT--DO NOT QUOTE OR CITE

250103204

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Chan et al. (1989)	134 children 7 yr. of age in London, England, <2,000 gr. birthweight; 123 controls with normal birthweight	Parental questionnaire	Wheeze and cough	OR = 2.7 (1.3-5.5) of having wheeze at age 7 in children of smoking mothers, OR = 2.4 (1.3-4.6) of having cough	Effects on wheeze independent of confounders. Effects on cough disappeared after controlling for confounders
Strachan et al. (1990)	A sample of 770 children from population described above	Salivary cotinine levels	Respiratory symptoms in children	No association with wheeze or cough. Association with frequency of chest colds ($p<0.01$)	
Krzyzanwoski et al. (1990)	298 children aged 5-15 yr. in Tucson, AZ	Parental questionnaire	Respiratory symptoms in children reported by parents	Increase in prevalence of "chronic bronchitis" in children exposed to ETS and formaldehyde	
Dijkstra et al. (1990)	1,051 6-12-yr. old children in The Netherlands	Parental questionnaire	Respiratory symptoms in children reported by parents	In children exposed to ETS at home: OR = 2.5 (1.1-5.6) for frequent cough; OR = 1.9 (1.0-3.5) for wheeze; OR = 2.0 (0.9-4.2) for shortness of breath	Independent of parental respiratory symptoms and maternal smoking during pregnancy

DRAFT--DO NOT QUOTE OR CITE

05/15/92

250103205

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

DRAFT--DO NOT QUOTE OR CITE

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Mertsola et al. (1991)	54 children aged 1-6 yr. with a history of wheezy bronchitis in Turku, Finland	Parental questionnaire	Incidence of prolonged wheezing episodes during follow-up of 4 mo.	OR = 4.8 (1.9-12.6) for children exposed to ETS	Independent of age, sex, number of siblings, medication, allergy

[a]95% confidence intervals in parentheses.

250103206

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-7. Recent epidemiologic studies of effects of passive smoking on asthma in childhood

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Burchfiel et al. (1986)	3,482 nonsmoking children 0-19 yr. in Tecumseh, MI	Questionnaire answered by subjects or parents	Prevalence of asthma	OR = 1.7 (1.2-2.5) for boys; OR = 1.2 (0.8-1.9) for girls	Independent of parental respiratory illness, age, parental education, family size, allergies
Evans et al. (1987)	191 children aged 4-17 yr. in New York, NY	Parental questionnaire	Emergency room visits and hospitalizations for asthma (from medical records)	3.1 ± 0.4 vs. 1.8 ± 0.3 ($p=0.008$) emergency room visits in children of smoking and non-smoking parents	No distinction made between maternal and paternal smoking. Independent of race and parental employment status
O'Connor et al. (1987)	292 subjects aged 6-21 yr. in Boston, MA	Parental questionnaire	Bronchial response to cold air	Significantly increased response in asthmatics whose mothers smoked	No increase in nonasthmatics whose mothers smoked
Murray and Morrison (1989)	415 children aged 1-17 yr. with asthma in Vancouver, Canada	Parental questionnaire	Asthma symptom score for severity of asthma	Higher scores ($p<0.01$) in children of smoking mothers	Stronger effect in boys and older children

DRAFT--DO NOT QUOTE OR CITE

05/15/92
25010320H7

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-7. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Krzyzanowski et al. (1990)	298 children aged 5-15 yr. in Tucson, AZ	Parental questionnaire	Parental reports of asthma in their children	OR = 9.0 (2.4-34.0) for children exposed to ETS and formaldehyde vs. nonexposed	Small sample
Sherman et al. (1990)	770 children aged 5-9 yr. followed for 11 yr. in Boston, MA	Parental and subject questionnaire	Physician diagnosis of asthma	No effect of parental smoking on prevalence or incidence of asthma	No effort to assess effect of heavy smoking by parents. No control for socio-economic status
Weitzman et al. (1990)	4,331 children aged 0-5 yr. (U.S. National Health Interview)	Maternal questionnaire	Asthma for at least 3 mo. at time of questionnaire	OR = 2.1 (1.3-3.3) for children whose mothers smoked ≥ 10 cig./day	Independent of race, sex, family size, presence of both parents, number of rooms
Oldigs et al. (1991)	11 asthmatic children	Direct exposure to ETS for 1 hour	Changes in lung function	No effect	No assessment of effect of chronic exposure

DRAFT--DO NOT QUOTE OR CITE

05/15/92 25010320H8

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-7. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Martinez et al. (1991b)	774 children aged 0-5 yr. followed for several years in Tucson, AZ	Parental questionnaire	Physician diagnosis of asthma	OR = 2.5 (1.4-4.6) for children of low maternal education whose mothers smoked ≥ 10 cig./day	No effect among children of better-educated mothers

[a]95% confidence intervals in parentheses.

DRAFT--DO NOT QUOTE OR CITE

05/15/92

250103209

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-8. Epidemiologic studies of effects of passive smoking on incidence of sudden infant death syndrome (SIDS)

Authors	Population studied	ETS exposure assessment	Results[a]	Observations
Steele and Langworth (1966)	80 infants who died of SIDS; 157 matched controls in Ontario, Canada	Maternal report from hospital record at birth	OR = 2.1 (1.1-3.8) when mother smoked 1-19 cig./day; OR = 3.6 (1.7-7.9) when mother smoked ≥ 20 cig./day	No control for socio-economic status or maternal age
Naeye et al. (1976)	59,379 infants born in several U.S. cities	Maternal report from hospital record at birth	OR = 1.6 (1.0-2.4) for any maternal smoking; OR = 2.6 (1.7-4.0) for mothers smoking ≥ 6 cig./day	Controlling for place of birth, date of delivery, gestational age, sex, race, socio-economic status
Bergman and Wiesner (1976)	100 cases of SIDS; 100 matched controls in King County, WA	Maternal questionnaire answered after death (or at equivalent age for controls)	OR = 2.4 (1.2-4.8). Effect only significant for mothers ≤ 25 yr. (OR = 4.4 [1.7-11.2])	Independent of maternal education, race, sex, birth date
Lewak et al. (1979)	44 cases of SIDS	Maternal questionnaire	OR = 4.4 (2.1-9.2)	No control for possible confounding factors
Malloy et al. (1988)	305,000 births in Missouri	Maternal reports on birth certificate	OR = 1.8 (1.4-2.2)	Controlling for marital status, maternal age, education, parity, and birthweight
Hoffman et al. (1988)	800 SIDS cases; 1,600 controls (NICHD cooperative study)	Maternal questionnaire	OR = 3.4 ($p<0.005$)	Controlling for age, birthweight, and race

DRAFT--DO NOT QUOTE OR CITE

05/15/92

250103205C

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-8. (continued)

Authors	Population studied	ETS exposure assessment	Results[a]	Observations
Haglund and Cnattingius (1990)	279,000 births in Sweden	Maternal questionnaire	OR = 1.8 (1.2-2.6). Heavy- smoking mother: OR = 2.7 (1.9-3.9)	Independent of birthweight, maternal age, social status, parity, sex, type of birth
Mitchell et al. (1991)	162 SIDS cases; 3-4 times as many controls	Parental questionnaire	OR 1-9 cig./day 1.9 (1.0-3.5) 10-19 cig./day 2.6 (1.5-4.7) ≥20 cig./day 5.1 (2.9-9.0)	Independent of prenatal care, maternal age, education, marital status, sex, neonatal problems, parity, birthweight, race, season of death, breastfeeding

[a]95% confidence intervals in parentheses.

DRAFT--DO NOT QUOTE OR CITE

250103205 1

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 7-9. Studies on pulmonary function referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Surgeon General	NRC
Berkey et al., 1986	7,834	Children (6-10)	X	X
Brunekreef et al., 1985	173	Adult women	X	
Burchfiel et al., 1986	3,482	Infants/children (0-10)	X	
Chen and Li, 1986	571	Children/adol. (8-16)	X	X
Comstock et al., 1981	1,724	Adults	X	
Dodge, 1982	558	Children (8-10)	X	X
Ekwo et al., 1983	1,355	Children (6-12)	X	
Ferris et al., 1985	10,000	Children/adol. (6-13)		X
Hasselblad et al., 1981	16,689	Children (5-17)	X	X
Kauffmann et al., 1983	7,818	Adults	X	
Kentner et al., 1984	1,851	Adults	X	
Lebowitz, 1984	117	Families	X	
Lebowitz and Burrows, 1976	271	Children/adol. (<16)	X	X
Schilling et al., 1977	816	Children/adol. (<18)	X	X
Tager et al., 1979	444	Children (5-19)		X
Tager, 1983	1,156	Children (5-9)	X	X
Tashkin et al., 1984	1,080	Children (7-17)	X	X
Vedal et al., 1984	4,000	Children (6-13)	X	
Ware et al., 1984	10,106	Children (6-13)		X
Weiss et al., 1980	650	Children (5-9)	X	X
White and Froeb, 1980	2,100	Adults	X	

250103205 2

05\15\92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-10. Recent epidemiologic studies on the effects of passive smoking on lung function in children

Authors	Population studied	ETS exposure assessment	Results[a]	Observations
O'Connor et al. (1987)	97 children (12.8 ± 0.3 yr.) of smoking mothers; 168 children (12.9 ± 0.2 yr.) of nonsmoking mothers in Boston, MA	Parental questionnaire	Nonsmoking mothers vs. smoking mothers: FEV_1 (% predicted) 108.0 ± 1.4 vs. 101.4 ± 1.1 ($p<0.001$). FEF_{25-75} (% predicted) 103.0 ± 2.3 vs. 88.2 ± 1.5 ($p<0.001$)	Independent of personal smoking habits
Lebowitz et al. (1987)	353 subjects aged 5.5-25 yr. in Tucson, AZ	Parental questionnaire	Smoking mothers vs. nonsmoking mothers FVC (residuals) +3.3 vs. -1.4 ($p<0.001$)	Interaction between family history of respiratory illnesses and passive smoking for $V_{max}50\%$ residuals
Tsimoyanis et al. (1987)	132 athletes exposed to ETS; 61 athletes not exposed to ETS	Self-reported exposure to ETS	OR of having low FEF_{25-75} 4.7 (1.1-20.8)	
Kauffmann et al. (1989b)	1,160 French children	Parental questionnaire	Loss of 10 ml of FEV_1, ($p=0.05$); Loss of 15 ml/sec of FEF_{25-75} ($p<0.01$)	Independent of sex, town of origin, age, height, weight, and family aggregation of lung function
Chan et al. (1989)	130 children of low birthweight at age 7 yr. in England	Maternal reports of cigarette smoking	Mean V_{max} 75% (% predicted) in exposed vs. nonexposed 80.7 vs. 91.4 ($p<0.01$)	Independent of sex, birthweight, neonatal respiratory illness, treatment

DRAFT--DO NOT QUOTE OR CITE

250103205 3
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-10. (continued)

Authors	Population studied	ETS exposure assessment	Results[a]	Observations
Dijkstra et al. (1990)	634 children aged 6-12 yr. in The Netherlands	Parental questionnaire	Decrease in: FEV_1 (-1.8% [-0.2 to -3.31]); $FEF_{25-75\%}$ (-5.21% [-1.4 to -8.8]); PF (-2.8% [0.6 to -4.8])	Independent of maternal smoking during pregnancy
Strachan et al. (1990)	757 children in Scotland	Salivary cotinine levels	Negative correlation with $FEF_{25-75\%}$ ($p<0.05$) and V_{max} 75% ($p<0.05$)	Approx. 7% difference between maximal exposure and no exposure
Martinez et al. (1991b)	774 children enrolled at age 0-5 in Tucson, AZ, and followed for several years	Parental questionnaire	15% lower levels of % predicted $FEF_{25-75\%}$ among children of mothers who smoked and had a low level of education	

[a]95% confidence intervals in parentheses.

DRAFT--DO NOT QUOTE OR CITE

250103205H
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-11. Recent epidemiologic studies on the effects of passive smoking on adult respiratory symptoms and lung function

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Svendsen et al. (1987)	1,245 married American nonsmoking men aged 35-57 yr.	Subject's report of spouse's smoking habits	FEV_1	Mean difference of 99 ml (5-192 ml)	No dose-response effect
Kalandidi et al. (1987)	103 Greek women with obstructive lung disease aged 40-79 yr; 179 control women; all nonsmokers	Subject's report of spouse's smoking habits	See population studied	OR = 1.9 (1.0-4.0)	No dose-response effect
Masi et al. (1988)	636 subjects aged 15-36 yr.	Subject's report of exposure to ETS	Maximal expiratory flows (MEF); diffusing capacity (DC)	Inverse relationship with ETS exposure at home in men for MEF; with exposure at work in women for DC	Strongest effect in men for exposure before age 17 yr.

DRAFT--DO NOT QUOTE OR CITE

05/15/92

2501032055

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 7-11. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[a]	Observations
Kauffmann et al. (1989a)	2,220 American women aged 25-69 yr; 3,850 French women aged 25-59 yr.	Subject's report of spouse's smoking habits	Self-report of respiratory symptoms; lung function	OR = 1.3 for wheezed in U.S. sample; OR = 1.4 for cough and OR = 1.2 for dyspnea in French sample; lower FVC and FEV_1 (p=0.01) in French women age ≥ 40 yr.	Increased risks for respiratory symptoms did not reach statistical significance
Hole et al. (1989)	7,997 subjects aged 45-64 yr. in Scotland	Questionnaires answered by household members	Cardiorespiratory symptoms. Lung function	No significant increase in risk of symptoms; decrease in FEV_1 (60 ml) when a cohabitee smoked > 15 cig./day	
Schwartz and Zeger (1990)	100 student nurses in Los Angeles, CA	Questionnaire answered by subject on presence of a smoking roommate	Respiratory symptoms assessed by self-administered questionnaire	Increased risk of having phlegm (OR = 1.4 [1.1-1.9])	Over-reporting by exposed subjects may bias results

[a]95% confidence intervals in parentheses.

DRAFT--DO NOT QUOTE OR CITE

2501032056
05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

8. ASSESSMENT OF INCREASED RISK FOR RESPIRATORY ILLNESSES IN CHILDREN FROM ENVIRONMENTAL TOBACCO SMOKE

In the preceding chapter, a review was presented of recently published studies regarding the association between respiratory illnesses in children and environmental tobacco smoke (ETS) exposure. The biological plausibility and the possible pathogenetic mechanisms involved in each group of illnesses included in the chapter were also discussed. The purpose of this chapter is to consider the weight of the evidence as a whole, to analyze in detail possible sources of systematic bias or confounding that may explain the observed associations, and to estimate the population impact of ETS-associated respiratory illnesses.

8.1. POSSIBLE ROLE OF CONFOUNDING

In the review of the available evidence indicating an association (or lack thereof) between ETS exposure and the different outcomes considered in this report, the possible role of several confounding factors was analyzed in detail (see Chapter 7). Such analysis will only be summarized here.

- Other indoor air pollutants (wood smoke, NO_2, formaldehyde, etc.) have not been found to explain the effects of ETS, but may interact with it to increase the risk of both respiratory illnesses and of decreased lung function in children.
- Many of the studies reviewed in this report and in those of the National Research Council (NRC) (1986) and the Surgeon General (U.S. DHHS, 1986) used either multivariate statistical methods of analysis or poststratification of the sample to control for the possible confounding effects of socioeconomic status. Others controlled for this effect by study design. It can be concluded that socioeconomic status does not explain the reported effects of ETS on children's health, although children belonging to some social groups may be at increased risk of suffering the effects of passive smoking (see also Section 8.3).
- The effect of parental symptoms on the association between ETS and child health has also been extensively analyzed. It can be concluded that, although parents with symptoms may be more aware of their children's symptoms than are parents without symptoms, it is unlikely that this fact by itself explains the association. In fact, objective parameters of lung function, bronchial responsiveness, and atopy,

25010320S7

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

which are not subject to such sources of bias, have been found to be altered in children exposed to ETS.

- The effects of passive smoking may be modified by several characteristics of the exposed child. Increased risk has been reported in premature infants and infants of low birthweight, infants who are not breast-fed, infants who are kept at home with smoking mothers and not sent to day-care centers, asthmatic children, and children who are active smokers.
- Maternal smoking during pregnancy has significant effects on fetal growth and development and may affect lung growth as well as the immunologic system. However, reports of important effects of paternal smoking on the child's health and studies in which ETS exposure was found to have effects that were independent of in utero exposure indicate that maternal smoking during pregnancy does not explain the relation between passive smoking and child health, but modifies the effects of ETS.

In summary, there is no single or combined confounding factors that can explain the observed respiratory effects of passive smoking in children.

8.2. MISCLASSIFICATION OF EXPOSED AND UNEXPOSED SUBJECTS

The importance of misclassification of exposed and unexposed children has not been addressed and will be analyzed in detail below.

Two possible sources of systematic bias related to subject misclassification are considered. The first is upward bias from the effect of active smoking in children; the second is downward bias due to misreporting and background exposure. Both have also been considered in the assessment of ETS and lung cancer in adults. Adjustment for background exposure will be similar to that presented in Chapter 6, except that data for increased incidence of some ETS-associated respiratory diseases show some evidence of thresholds that must also be taken into account.

8.2.1. Effect of Active Smoking in Children

The possibility needs to be considered that some children may be smokers themselves and that this may happen more often among children of smoking parents than among those of nonsmoking parents. This would bias the results upwards or against the null effect. This source of bias is only applicable to studies of older children; regular active smoking may occur but is rare before early adolescence. A study of third graders in Edinburgh, Scotland, by Strachan and

2501032058

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

coworkers (Strachan et al., 1989, see Section 7.4.1), for example, showed that salivary cotinine levels compatible with active smoking were found in 6 of 770 children ages 6-1/2 to 7-1/2 years, suggesting only a small potential for bias. Consideration should also be given to the fact that some of the effects described in Chapter 7 (for example, the increased risks for acute respiratory illnesses [Section 7.3.1] and for cough, phlegm, and wheezing [Section 7.5.1]) have been found to be stronger in younger children (i.e., those less likely to be active smokers) than in older children. This observed reduced effect with increasing age may be in part due to an age-related increase in misclassification of exposed subjects as "unexposed" (see below), but it is clear that these specific effects of ETS *do not increase with age*, as would be expected if active smoking biased the results of studies of ETS effects in older children. It can thus be concluded that the association between respiratory health in children and ETS is not attributable to active smoking by some children. It has been suggested that active and passive smoking may interact to increase the effects of either exposure separately (Lebowitz, 1988). This interaction is biologically plausible, because it is likely that active smoking may be more harmful in children whose lungs have been previously affected by ETS (see Section 7.1).

8.2.2. Misreporting and Background Exposure

Various investigators have measured cotinine levels in body fluids in infants and children and correlated the results with parental reports of ETS exposure. Coultas and coworkers (1987) reported that 37% of children under 5 years of age whose parents were both nonsmokers had a salivary cotinine level greater than 0, compared with 32% of children ages 6 to 12 and with 35% of children ages 13 to 17. These authors did not ask parents to report possible sources of ETS exposure for their children other than their own tobacco consumption. Strachan and coworkers' study in 6-1/2- to 7-1/2-year-old children in Scotland (Strachan et al., 1989) showed that 73% of children from households with no smokers had detectable concentrations of cotinine in saliva, whereas only 1 in 365 children from households with one or more smokers had no detectable salivary cotinine. The assay used by Strachan and coworkers was 10 times more sensitive than that used by Coultas and coworkers, and this may explain the larger number of subjects with detectable levels in the former study when compared to the latter.

Greenberg and coworkers (1984) studied cotinine levels in 32 infants in North Carolina with reported exposure to tobacco smoke within the previous 24 hours and in 19 unexposed infants. All subjects were under 10 months old. Urine samples of all exposed infants contained

2501032059

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

cotinine, whereas all unexposed infants except 2 (11%) had undetectable urine cotinine or levels below those of exposed infants with the lowest levels of urine cotinine. This same group of researchers reported results for a larger sample (433 infants at a mean age of 18 days) of the same population (Greenberg et al., 1989). They found that, of 157 infants who reportedly lived in nonsmoking households and were also not in contact with smokers the previous week, 37 infants (24%) had cotinine in their urine. They concluded that these infants had contact with tobacco smoke during the previous week and that this contact was unknown to or was not reported by their mothers.

Greenberg and coworkers (1991) followed 152 of the 433 infants originally enrolled and reassessed exposure to ETS (through maternal interviews) and urine cotinine levels when the child was 12.3 ± 0.6 months old. They found a significant increase in the prevalence of tobacco smoke absorption, indicated by excretion of cotinine, during the first year of life (from 53% at a mean age of 3 weeks to 77%). The interviews showed that this was mainly due to an increased exposure to nonhousehold sources of smoke (from 14% to 36%). The proportion of infants who reportedly had no contact with smokers but had cotinine in their urine increased from 24% at 3 weeks to 49% at 1 year of age.

These results indicate that studies that rely exclusively on parental questionnaires to ascertain ETS exposure in children may misclassify many exposed subjects as nonexposed. Moreover, the degree of misclassification may increase with the child's age.

The possible consequences of this misclassification of exposure need to be discussed in detail. Nondifferential misclassification (i.e., exposure classification that is incorrect in equal proportions of diseased and nondiseased subjects) biases the observed results towards a conclusion of no effect (Rothman, 1988; see below). The effect of differential misclassification depends on the direction in which misclassification occurs. If true ETS exposure is preferentially reported by parents of diseased subjects (i.e., there is reporting bias), an excess of disease prevalence would be found among exposed subjects when compared to unexposed subjects that is unrelated to any biological effect of ETS. The evidence available clearly indicates that this is a very unlikely explanation for the reported misclassification of ETS exposure in infants and children. In fact, reporting bias cannot explain the substantial increase in "underreporting" of exposure with age. The logical explanation is provided by the finding that exposure to nonhousehold smokers increases significantly with age and parallels the increase in the proportion of subjects who have cotinine in their urine (Greenberg et al., 1991). There is no reason to believe that exposure to smokers may occur preferentially among diseased children, and the contrary may be more

2501032060

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

reasonable; the increased awareness of the ill effects of ETS inhalation may induce parents to limit contact between their diseased children and nonhousehold smokers. Thus, the net effect of misclassification of exposure, both nondifferential and differential, should be a systematic downward bias or bias toward observing no effect. A correction for the nondifferential misclassification bias of background exposure is made below.

8.3. ADJUSTMENT FOR BACKGROUND EXPOSURE

An important conclusion of the previous discussion is that studies based on parental questionnaires may underestimate the health risk from ETS in children due to underreporting of ETS exposure. The NRC report on passive smoking (NRC, 1986) adopted the use of cotinine measures to correct for misreporting of ETS exposure for lung cancer effects, and this approach was adapted for use in Chapter 6 of this report. It will also be employed here, with the cotinine ratios, however, based on exposure data in children rather than in adults. The method is based on several assumptions: (1) cotinine concentrations in body fluids of nonsmokers are linearly related to ETS exposure, (2) the excess risk of respiratory illness in subjects exposed to ETS is linearly related to the dose of ETS absorbed, (3) the relationship between ambient and absorbed ETS is linear, and (4) one cotinine determination may adequately represent average childhood exposure to ETS. While considerable evidence exists for assumptions 1 through 3, there is now some evidence that assumption 4 may not be entirely warranted. Coultas and coworkers (1990b) in a small study of 9 children from 10 homes with at least 1 smoker reported that there is considerable variability in cotinine levels in body fluids within individuals exposed to ETS when such levels are repeatedly measured in different days. Thus, while the method of adjustment is based on group mean body cotinine levels, which apparently reflect well household ETS levels (see below), the intraindividual variability may subject these means to some error.

Application of the algorithms proposed by the NRC requires some knowledge of Z, the ratio between the operative mean dose level in the "exposed" group, d_E, and the mean dose level in the "unexposed" group, d_N. $RR(d_E)$, the relative risk for the group identified as "exposed" compared to the group identified as "unexposed", is thus given by

$$RR(d_E) = (1+Z^*\beta d_N)/(1+\beta d_N) \qquad (8-1)$$

where β is the amount of increase per unit dose and $Z > RR(d_E) > 1$. (The "unexposed" group actually contains those with background exposure plus those truly unexposed.)

250103206

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Several studies are available that could be used for the purpose of estimating Z. Jarvis and coworkers (1985) studied 569 nonsmoking schoolchildren ages 11 to 16 in Great Britain. The investigators reported that, when compared to salivary cotinine levels in children of nonsmoking parents (N = 269), mean levels of salivary cotinine were 3.0 times as high in children whose father smoked (N = 96), 4.4 times as high in children whose mother smoked, and 7.7 times as high in children whose parents were both smokers. Pattishall and coworkers (1985) reported that children from homes with smokers (N = 20) had 4.1 times as high mean levels of serum cotinine as children from nonsmoking families. Black children, however, in the same study had lower values of Z (2.8) than did white children. Coultas and coworkers (1987) found that, among 600 U.S. children up to age 17 years, mean salivary cotinine levels were between 1.3 and 2.6 times as high among subjects exposed to one cigarette smoker at home as among unexposed subjects, and between 2.9 and 3.5 times as high among subjects exposed to two or more smokers at home as among subjects not exposed to cigarette smokers at home. Strachan and coworkers (1989) reported separate results for 6-1/2- to 7-1/2-year-old Scottish children belonging to families living in their own homes and for those belonging to families living in rented homes. In the former, geometric mean salivary cotinine was 6 times as high among subjects exposed to one cigarette smoker at home as among unexposed subjects and 16 to 17 times as high among subjects exposed to two or more smokers at home as among unexposed subjects. For children belonging to families living in rented homes, the same ratios were 3 to 5.5 times and 4 to 7 times, respectively.

While these studies show consistent relationships between mean body cotinine levels in children and home smoker occupancy, there is also a wide variability in the estimated Z ratios, ranging from 1+ to 17. These different estimates may have very important effects on the background exposure adjustment and, thus, on the calculation of adjusted relative risks for different studies (see also Chapter 6). For example, for a study in which the observed relative risk (RR) is 2.0 but for which the Z ratio is 3, equation 8-1 can be solved for βd_N, which is the estimated increase in relative risk for the group called "unexposed" but who in fact have been exposed to some recent ETS. Solving,

$$\beta d_N = 1.$$

Thus, the adjusted RR for the group identified as "unexposed" would be 2. and the adjusted RR for an "exposed" group compared to a truly unexposed group would be 1 + (3*1) = 4, i.e., twice the observed risk. For a similar example (observed RR = 2) but with Z = 5, $\beta d_N = 0.3$, the RR for a

250103209

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

group identified as "unexposed" in this case would be 1.3, and the adjusted RR for an "exposed" to a truly unexposed group would be 2.67. Finally, if the observed RR is still 2 but Z = 17, βd_N = 0.07, RR for "unexposed" would be 1.07 and the adjusted RR for exposed children would be 2.13. These results are shown in Table 8-1.

These calculations show that when use of parental questionnaires significantly underestimates their children's exposures to other sources of ETS (other than via the parental ETS) and values of Z are lower (as found in black children by Pattishall and coworkers [1985], and in children of lower socioeconomic status by Strachan and coworkers [1989]), the "true" RR of children exposed to ETS may be considerably underestimated. But perhaps the most important conclusion that may be derived from the above analysis is that exposure to ETS from sources other than smoking parents may be high enough to constitute a significant risk for their health. This may be particularly consequential for children of lower socioeconomic levels, whose nutritional status, crowding conditions at home, and opportunity for contact with biological agents of disease make them a part of the population that is particularly susceptible to respiratory illnesses during infancy and childhood. Available data show that ETS exposure via nonhousehold members in these children, as measured by cotinine levels in body fluids, may be as much as one-third that of children exposed to one smoking parent (Z = 3). In the example presented above (observed RR = 2), the estimate of the adjusted relative risk is 4 for children of smoking parents to the truly unexposed children. However, using the same assumptions, children of *nonsmoking parents* who are exposed to ETS (at background levels found in some of the studies) would have twice as high a risk of developing the illness under study as children truly unexposed to ETS.

A cautionary note about the model is appropriate. Table 8-1 shows that, for observed RR = 2 and Z = 3, the adjusted relative risk is 4. However, as the observed RR and Z get closer together, the behavior of the model becomes erratic. This is shown in Table 8-2. In fact, the model (equation 8-1) becomes undefined if Z is less than or equal to the observed RR, and it reaches some stability only as Z becomes at least 30% to 50% greater than RR.

Fortunately, the estimates of Z presented above are appreciably greater than the observed relative risk estimates seen in Chapter 7, and in the observed range of both RR and Z, the model yields relatively stable estimates of the adjusted RR. Furthermore, as discussed in Chapter 6, the values of RR and Z are expected to be correlated for each study, i.e., the greater the Z ratio between exposed and unexposed groups in each study, the greater should be the observed RR and the less the effect of the (equation 8-1) adjustment.

2501032063

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

If the above model is correct, then exposure of children to ETS other than at home (parental smoking) may be an important risk factor for respiratory illness in childhood. On the other hand, it is also possible that for at least some respiratory illnesses, outside exposure to ETS has relatively little effect, either because outside exposures in younger children tend to be less than those of older children or because there may be a threshold of exposure below which certain respiratory effects may not be expected to occur. For this latter case, equation 8-1 is not an appropriate model, and the observed relative risk would be taken to be the true risk. Both models are addressed in the sections that follow.

8.4. ASSESSMENT OF RISK

Neither the NRC report (1986) nor the Surgeon General's report (U.S. DHHS, 1986) attempted to assess the population or public health impact of the increased risk of respiratory disorders in children attributable to ETS exposure. In this section, estimates will be derived for the number of ETS-attributable lower respiratory tract infections in infants and for the induction and exacerbation of childhood asthma. Quantifying the public health impact of other conditions, such as reduced lung function, coughing, wheezing, and middle ear effusion, is difficult, either because of the lack of overt symptoms or because some necessary U.S. population health statistics are not available. Estimates of sudden infant death syndrome (SIDS) deaths attributable to ETS will not be made but will be discussed in Section 8.4.3.

For the following quantitative analyses, estimates will be developed in terms of ranges. The ranges are derived by the use of both threshold and nonthreshold (equation 8-1) models, different estimates for population incidence and prevalence, and estimated values of Z and RR from studies reviewed above. Various differences in design, disease definition, and conduct among these studies make them less adaptable to meta-analysis techniques than were the lung cancer studies. To the extent that a less rigorous statistical analysis is attempted here, the ranges should reflect that uncertainty.

8.4.1. Asthma

From the analysis of studies regarding risk for asthma and ETS exposure, it was concluded that passive smoking increases both the number and severity of episodes in asthmatic children. It was further concluded that ETS is a risk factor for new cases among previously asymptomatic children, since the evidence is suggestive, but not conclusive, of a causal association (see Section 7.6). Relative risks for asthma ranged from 1.0 to 2.5 in the studies analyzed, but methodologies

250103206H

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

differed considerably among studies, and effects were often found only in children of mothers who smoke heavily. Of the four large studies, totaling over 9,000 children (Burchfiel et al., 1986; Sherman et al., 1990; Weitzman et al., 1990; Martinez et al., 1991b), three showed statistically significant risk estimates ranging from 1.7 to 2.5, with the two largest ratios, 2.5 (Martinez et al., 1991b) and 2.1 (Weitzman et al., 1990), coming from comparisons using children of heavily smoking mothers (≥ 10 cig./day) as the exposed group. The third study (Burchfiel et al., 1986) had OR = 1.7 for males with two smoking parents, but results were not significant either for girls or for children with one parental smoker. The fourth study (Sherman et al., 1990) (770 children) did not find an effect, but made no effort to assess the effect of heavy smoking by parents, nor was there control for socioeconomic status. Thus, assigning a range of 1.75 to 2.25 for the estimated relative risk of developing asthma for children of mothers who smoke 10 or more cigarettes per day appears reasonable and is within the ranges of observed risk.

The above results suggest two possible scenarios. One scenario is that relatively heavy exposure to ETS is needed to bring on asthma, i.e., there is a threshold of exposure below which effects will not occur. Alternatively, lesser exposures may merely induce fewer effects, not detectable statistically with these study designs. The choice of scenario does not affect the observed relative risk but will affect whether or not an adjustment for background exposure (Z ratio) is appropriate. Under the first (threshold) scenario, the estimates of RR = 1.75 to 2.25 need no adjustment; under the alternative (nonthreshold) scenario, equation 8-1 applies.

Considering the nonthreshold model first, from the discussion in Section 8.3, it can be assumed that values of 3 to 10 may be a reasonable range for estimates of Z (i.e., the ratio of body cotinine levels in children whose mothers smoke heavily to those of children whose mothers do not smoke). Lower values of Z would yield significantly larger estimates of asthma cases attributable to ETS. Based on the above estimates for a range of Z and RR and use of the nonthreshold model, the estimated range of adjusted relative risks for children of mothers who smoke 10 or more cigarettes per day would be approximately 1.91 to 6.00 (see Table 8-3). Transforming relative risks to attributable risks (Rothman, 1986), 48% to 83% of all cases of asthma among children of mothers who smoke 10 or more cigarettes per day may be attributable to passive smoking based on

$$AR_E = 100 * (1 - [1/RR]) \qquad (8\text{-}2)$$

where AR_E is the attributable risk (%) for the exposed population.

2501032065

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Under the assumptions of the threshold model, RR = 1.75 to 2.25 for children of heavily smoking mothers, and the AR_E = 43% to 56% (see Table 8-3); for children of light smoking mothers, RR = 1, and the AR_E = 0.

To calculate the percentage of all cases occurring in a mixed population of exposed and unexposed individuals that is attributable to exposure (AR_T), knowledge of the prevalence of mothers smoking 10 or more cigarettes per day is needed because

$$AR_T = AR_E * P_I \qquad (8\text{-}3)$$

where P_I is the proportion of cases that is exposed (Rothman, 1986). It has been reported that approximately 26% of the population of women of childbearing age smoked in the United States in 1988 (CDC, 1991b) and in 1990 (CDC, unpublished). For the number of cigarettes smoked, Weitzman and coworkers (1990), using the 1981 National Health Information Survey (NHIS), found that approximately 50% of smoking mothers of children ages 0 to 5 years smoke 10 or more cigarettes per day. The 1990 NHIS reports that 78% of smoking women ages 18 to 44 smoke at least 10 cigarettes per day (data courtesy of Dr. Gary Giovino, CDC, unpublished). We have used an average of 65% to derive the estimates in Table 8-3. Based on these figures and the threshold model, it can thus be estimated that approximately 7% to 9% of all cases of asthma may be attributable to exposure to ETS from mothers who smoke 10 or more cigarettes per day. Estimates of the prevalence of asthma among U.S. children less than age 18 vary from 5% to 10% (Clark and Godfrey, 1983) to 3% to 8% (R. Evans et al., 1987), depending on disease definition. This latter paper uses the data from the 1979-1981 NHIS and derives a population asthma prevalence of 2 million to 5 million. A more recent estimate from the 1989 NHIS is 3.9 million (U.S. DHHS, 1990b). Use of these population prevalence figures and the threshold model provides a range of 8,000 to 26,000 as the annual number of new cases of childhood asthma attributable to mothers who smoke 10 or more cigarettes per day. The confidence in this estimate is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

If the nonthreshold model applies, use of the same prevalence figures leads to a range of 13,000 to 60,000 new cases per year attributable to all ETS exposures (Table 8-3).

While the range of 8,000 to 60,000 is plausible, the existing data are more supportive of the threshold model, which assumes that rather heavy exposures to ETS are required to induce asthma in previously asymptotic children (Section 7.6.2). Thus, the range of 8,000 to 26,000 will be

25010320666

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

adopted as the more probable range of new cases among children per year attributable to ETS exposure.

In view of the increased number and severity of asthmatic episodes also caused by ETS, the public health impact of ETS on asthmatic children is considerably greater than the range of estimates for new cases presented above. Shephard (1992), after reviewing several studies, concludes that ETS exposure (from any source) exacerbates preexisting asthma in approximately 20% of patients. If this figure is correct, up to 1 million asthmatic children could be affected. Also, in an earlier study, O'Connell and Logan (1974) found that parental smoking aggravated clinical symptoms of 67% of 265 asthmatic children in the Midwest versus 16% of 137 controls ($p < 0.0001$) and that 10% of 400 asthmatic patients (of both smoking and nonsmoking parents) considered tobacco smoke a major aggravating factor. D. Evans and coworkers (1987) found that passive smoking by asthmatic children in New York City (via presence of smokers in the household) was associated with a mean annual increase of 1.34 emergency room visits per year for asthmatic symptoms, an increase of 63% over asthmatic children from nonsmoking households. Thus, exposure to ETS in general and especially to parental ETS adversely affects hundreds of thousands of asthmatic children.

8.4.2. Lower Respiratory Illness

From the assessment of available data (see Section 7.3), it was concluded that exposure of infants and young children to ETS causes an increased incidence of lower respiratory illness (LRI). An examination of the data in the referenced studies of both Tables 7-1 and 7-2 leads to the conclusion that the observed risk of having LRIs is approximately 1.5 to 2.0 times as high in young children whose mothers smoke as in those whose mothers do not smoke and that the risk is probably higher in infants than in toddlers.

This estimate is also consistent with that of the NRC (1986), which estimated a relative risk of up to 2 for infants who have one or more parents who smoke. The more recent evidence reviewed here strongly suggests that the increased risk due to ETS exposure lasts for at least the first 18 months and decreases after that. Based on this evidence, this chapter estimates a relative risk range of 1.5 to 2.0 for infants and children up to 18 months old who have smoking mothers. It will assume that the increased risk is zero after 18 months.

Based on these findings, and following equation 8-1 with a range of $Z = 3$ to 10 and $RR = 1.5$ to 2.0, the adjusted relative risk range becomes 1.6 to 4.0, and AR_E takes the range 38% to 75%. As in the previous section, for equation 8-3, the mixed population attributable risk AR_T

250103206?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

takes the range 10% to 20%, again based on 1988 and 1990 estimates of approximately 26% women of childbearing age who smoked (CDC, 1991b; CDC, unpublished). Because the estimated mean number of cigarettes smoked by these women is approximately 17 to 20 per day (CDC 1991b; CDC, unpublished), it is reasonable to assume that most children of smoking mothers will be exposed. Therefore, the proportion of cases exposed, P_1, is estimated to be 0.26.

It has recently been shown that the incidence of LRIs early in life is approximately 30% (Wright, 1991). When the analysis is limited to the first 18 months of life, the population at risk is approximately 5.5 million children. Application of the same algorithms described above yields 150,000 to 300,000 cases of LRIs annually in children under 18 months old attributable to exposure to ETS generated mostly by smoking mothers. Approximately 5% of these LRIs require admission to a hospital (Wright, 1989), and therefore, it is estimated that 7,500 to 15,000 hospitalizations yearly for LRIs may be attributable to ETS exposure.

While these estimates may appear large, three factors suggest that they are on the low side. First, although these estimates are calculated only for children less than 18 months old, Section 7.2 presents evidence that these ETS-attributed increased risks extend at a decreasing rate up to 3 years of age. Second, no estimates have been calculated for exposure in a smoking father-nonsmoking mother household. Third, these numbers do not take into account the fact that many infants and young children have recurrent LRIs, and therefore, more than one episode of such illnesses may be attributable to ETS in each exposed child.

8.4.3. Sudden Infant Death Syndrome

Because this report concludes that there is an association between maternal smoking and SIDS but is unable to determine the contribution that ETS makes to that association (see Section 7.7), no estimate of ETS-attributable SIDS deaths will be calculated. The Centers for Disease Control (CDC) (1991a) provides an estimate of 702 SIDS deaths attributable to maternal smoking, based on a relative risk of 1.5 for infants of actively smoking mothers. While this report concurs with the numbers and the methodology used to determine that estimate, it is unable to apportion the in utero, lactation, and ETS exposure components of the risk.

8.5. CONCLUSIONS

This chapter has attempted to estimate the U.S. population impact of ETS exposure on childhood asthma and lower respiratory tract infections in young children. For new cases of asthma in previously symptomatic children under 18 years of age, we estimate that 8,000 to 26,000

2501032068

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

is a probable range of new cases per year that are attributable to ETS exposure from mothers who smoke at least 10 cigarettes per day. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

While the data are most supportive of a situation in which heavy exposures to ETS are required to induce new cases of asthma, two other scenarios would lead to larger estimates. The first is that even in the absence of smoking mothers, a child could receive heavy ETS exposure from other sources. The second is that lesser ETS exposures induce lesser numbers of new cases, and the increase is not statistically detectable. Under this latter (nonthreshold) scenario, the range of new cases of asthma annually attributable to ETS exposure is 13,000 to 60,000.

This report concludes that, in addition to inducing new cases of asthma, ETS exposure increases the number and severity of episodes among this country's 2 million to 5 million asthmatic children. This chapter considers exposure to parental smoking to be a major aggravating factor to approximately 10%, or 200,000, asthmatic children. Estimates of the number of asthmatics whose condition is aggravated to some degree by ETS exposure are very approximate but could run well over 1 million.

This chapter also estimates that 150,000 to 300,000 cases annually of lower respiratory tract infections in children up to 18 months old are attributable to ETS exposure, most of which comes from smoking parents (mostly mothers). These ETS-attributable cases are estimated to result in 7,500 to 15,000 hospitalizations annually. Confidence in these estimates is high based on the conclusion of a causal association and the strong validity of parental smoking as a surrogate of temporally-relevant ETS exposure in infants and young children. Additional cases and hospitalizations are expected to occur in children up to 3 years old in decreasing numbers, but this report makes no further quantitative estimates.

Infants' exposure to ETS may also be responsible for a portion of the more than 700 deaths from SIDS attributable to maternal smoking by the CDC (1991a), but this report is unable to determine whether and to what extent these deaths can be attributed specifically to ETS exposure.

The estimates of population impact presented above are given in ranges and approximate values to reflect the uncertainty of extrapolating from individual studies to the population. As with the lung cancer population impact assessment (Chapter 6), these extrapolations are all based on human studies conducted at true environmental levels. Therefore, they suffer from none of the uncertainties associated with either animal-to-human or high-to-low exposure extrapolations.

In addition to the estimates presented above, ETS exposure in children also leads to reduced lung function, increased symptoms of respiratory irritation, and increased prevalence of

2501032069

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

middle ear effusion, but this report does not provide estimates of the population impact of ETS exposure for these conditions.

250103207D

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table 8-1. Adjusted relative risks for "exposed children." Adjusted or background exposure based on body cotinine ratios between "exposed" and "unexposed" and equation 8-1

OBSERVED RELATIVE RISKS (RR)	Z RATIO OF BODY COTININE LEVELS ("EXPOSED"/"UNEXPOSED")							
	1.50	2.00	3.00	5.00	7.00	10.00	13.00	17.00
1.0	1	1	1	1	1	1	1	1
1.50	-	3.00	2.00	1.71	1.64	1.59	1.57	1.55
1.75	-	7.00	2.80	2.15	2.00	1.91	1.87	1.84
2.00	-	-	4.00	2.67	2.40	2.25	2.18	2.13
2.50	-	-	10.00	4.00	3.33	3.00	2.86	2.76
3.00	-	-	-	6.00	4.50	3.86	3.60	3.43

Table 8-2. Behavior variations in adjusted relative risks from equation 8-1 when the observed relative risks and Z ratios are close together

OBSERVED RELATIVE RISKS (RR)	Z RATIO							
	1.50	1.75	2.00	2.25	2.50	2.75	3.00	10.00
1.50	-	4.50	3.00	2.50	2.25	2.10	2.00	1.59
1.75	-3.5	-	7.00	4.38	3.50	3.06	2.80	1.91
2.00	-2.0	-6.00	-	10.00	6.00	4.67	4.00	2.25
2.25	-1.5	-3.38	-9.00	-	13.50	7.88	6.00	2.62
2.50	-1.25	-2.50	-5.00	-12.50	-	17.50	10.00	3.00

25010320?1

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

TABLE 8.3 Range of Estimates of Adjusted Relative Risk and Attributable Risk for Asthma Induction in Children ased on Both Threshold[1] and Nonthreshold Models[2]

	Threshold Model[1]		Nonthreshold Model[2]				
Observed Relative Risk	1.75	2.25	1.75	2.25	1.75	2.00	2.25
Adjusted Relative Risk[3]	-	-	1.91+	2.62+	2.80*	4.00*	6.00*
AR_E[4]	0.43	0.56	0.48	0.62	0.64	0.75	0.83
AR_T[5] (P_I[6]=0.17)	0.07	0.09	-	-	-	-	-
AR_T (P_I[7]=0.26)	-	-	0.12	0.16	0.17	0.20	0.22
ETS-Attributable Population Impact[8]	8,000 to 20,000	10,000 to 26,000	13,000 to 34,000	18,000 to 45,000	19,000 to 46,000	22,000 to 54,000	24,000 to 60,000

1. Threshold model assumes that heavy ETS exposure (i.e., mothers smoking $\geq$ 10 cig./day) is required to induce new cases.
2. Nonthreshold model assumes that all ETS exposure can produce some new cases of asthma.
3. Equation 8-1.
4. Attributable risk fraction for the exposed population.
5. Attributable risk fraction for the total (mixed) population.
6. Proportion of women of reproductive age who smoke at least 10 cigarettes per day. (0.26 x 0.65)
7. Proportion of women of reproductive age who smoke cigarettes.
8. Range based on 2 million to 5 million asthmatic children under 18 years old in the United States.

\+ Ratio of mean body cotinine levels: Z = 10
* Ratio of mean body cotinine levels: Z = 3

DRAFT--DO NOT QUOTE OR CITE

05/15/92
250103207?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

SELECTED BIBLIOGRAPHY

Note: This section includes all references cited in the document as well as additional references that were reviewed during the preparation of this document. This is not intended to be a comprehensive list of all references available on the topic.

Adams, J.D.; O'Mara-Adams, K.J.; Hoffmann, D. (1987) Toxic and carcinogenic agents in undiluted mainstream smoke and sidestream smoke of different types of cigarettes. Carcinogenesis 8(5):729-731.

Aguayo, S.M.; Kane, M.A.; King, T.E.; Schwarz, M.I.; Grauer L.; Miller, Y.E. (1989) Increased levels of bombesin-like peptides in the lower respiratory tract of asymptomatic cigarette smokers. J. Clin. Invest. 84:1105-1113.

Akiba, S.; Kato, H.; Blot, W.J. (1986) Passive smoking and lung cancer among Japanese women. Cancer Res. 46:4804-4807.

Alderson, M.R.; Lee, P.N.; Wang, R. (1985) Risks of lung cancer, chronic bronchitis, ischaemic heart disease and stroke in relation to type of cigarette smoked. J. Epidemiol. Community Health 39:286.

Alfheim, I.; Ramdahl, T. (1984) Contribution of wood combustion to indoor air pollution as measured by mutagenicity in Salmonella and polycyclic aromatic hydrocarbon concentration. Environ. Mol. Mutagen. 6:121-120.

Almanac of the 50 States. (1989) Hornon, E.R., ed. Palo Alto, CA: Information Publications.

American Academy of Pediatrics (1986) (p. 1-7).

Anderson, L.J.; Parker, R.A.; Strikas, R.A.; et al. (1988) Day-care center attendance and hospitalization for lower respiratory tract illness. Pediatrics 82:300-308.

25010320 73 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Andrae, S.; Axelson, O.; Bjorksten, B.; Fredriksson, M.; Ljellman, N-IM. (1988) Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors. Arch. Dis. Child. 63:473-478.

Aoki,_; et al. (1987) Smoking and Health. _. Elsevier Science Publishers B.V. (Biomedical Division), pp. 483-486.

Arundel, A.; Sterling, T.; Weinkam, J. (1987) Never smoker lung cancer risks from exposure to particulate tobacco smoke. Environ. Intl. 13:409-426.

Badre, R.; Guillerm, R.; Abran, N.; Bourdin, M.; Dumas, C. (1978) Atmospheric pollution by cigarette smoking. Ann. Pharm. Fr. 36:443-452.

Basrur, P.K.; McClure, S.; Zilkey, B. (1978) A comparison of short term bioassay results with carcinogenicity of experimental cigarettes. In: Nieburgs, H.E., ed. Prevention and detection of cancer, Part 1, Vol. 2, New York: Marcel Dekker, pp. 2041-2048.

Bellofiore, S.; Eidelman, D.H.; Macklem, P.T.; Martin, J.G. (1989) Effects of elastase-induced emphysema on airway responsiveness to methacholine in rats. J. Appl. Physiol. 66:606-612.

Benner, C.L.; Bayona, J.M.; Caka, F.M.; Tang, H.; Lewis, L.D.; Eatough, D.J. (1989) Chemical composition of environmental tobacco smoke. 2. Particle-phase compounds. Environ. Sci. Technol. 23:688-699.

Bergman, A.B.; Wiesner, B.A. (1976) Relationship of passive cigarette-smoking to sudden infant death syndrome. Pediatrics 58:665-668.

Berkey, C.S.; Ware, J.H.; Dockery, D.W.; Ferris, B.G., Jr.; Speizer, F.E. (1986) Indoor air pollution and pulmonary function in preadolescent children. Am. J. Epidemiol. 123:250-260.

Bernfeld, P.; Homburger, F.; Soto, E.; Pai, K.J. (1979) Cigarette smoke inhalation studies in inbred Syrian golden hamsters. J. Natl. Cancer Inst. 63:675-689.

2501032074

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Best, E.W.R.; Josie, G.H.; Walker, C.B. (1961) A Canadian study of mortality in relation to smoking habits. A preliminary report. Can. J. Public Health 52:99-106.

Bewley, B.R.; Halil, T.; Snaith, A.H. (1973) Smoking by primary schoolchildren: prevalence and associated respiratory symptoms. Br. J. Prev. Soc. Med. 27:150-153.

Bisgaard, H.; Dalgaard, P.; Nyboe, J. (1987) Risk factors for wheezing during infancy: a study of 5953 infants. Acta Paediatr. Scand. 76:719-726.

Black, N. (1984) Surgery for glue ear—a modern epidemic? Lancet i:835-837.

Black, N. (1985) The etiology of glue ear—a case-control study. Int. J. Pediatr. Otolaryngol. (Stockholm) 9:121-133.

Bland, M.; Bewley, B.R.; Pollard, V.; Banks, N.M. (1978) Effect of children's and parents' smoking on respiratory symptoms. Arch. Dis. Child. 53:100-105.

Blot, W.J.; Fraumeni, J.F. (1986) Passive smoking and lung cancer. J. Natl. Cancer Inst. 77(5):993-999.

Breese-Hall, C.; Hall, J.H.; Gala, C.L.; MaGill, F.B.; Leddy, J.P. (1984) Long-term prospective study in children after respiratory syncytial virus infection. J. Pediatr. 105:358-364.

Breslow, N.E.; Day, N.E. (1980) Statistical methods in cancer research. Lyon: IARC Sci. Publ. No. 32.

Britten, N. (1988) Validity of claims to lifelong non-smoking at age 36 in a longitudinal study. Int. J. Epidemiol. 17(3):525-529.

Bross, I.D.J.; Gibson, R. (1968) Risk of lung cancer in smokers who switch to filter cigarettes. Am. J. Public Health 58:1396-1403.

250103207S

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Brown, C.C.; Chu, K. (1987) Use of multistage models to infer stage affected by carcinogenic exposure: example of lung cancer and cigarette smoking. J. Chronic Dis. 40(2):171A-179A.

Brownson, R.C.; Reif, J.S.; Keefe, T.J.; Ferguson, S.W.; Pritzl, J.A. (1987) Risk factors for adenocarcinoma of the lung. Am. J. Epidemiol. 125:25-34.

Brunekreef, B.; Boleij, J.S.M. (1982) Long-term average suspended particulate concentrations in smokers' homes. Int. Arch. Occup. Environ. Health 50:299-302.

Brunekreef, B.; Fischer, P.; Remijn, B.; Van der Lende, R.; Schouten, J.; Quanjer, P.H. (1985) Indoor air pollution and its effects on pulmonary function of adult non-smoking women. III. Passive smoking and pulmonary function. Int. J. Epidemiol. 14:227-230.

Brunnemann, K.D.; Hoffmann, D.; Wynder, E.L.; Gori, G.B. (1976) Chemical studies on tobacco smoke: 37. Determination of tar, nicotine, and carbon monoxide in cigarette smoke. A comparison of international smoking conditions. In: Wynder, E.L.; Hoffmann, D; Gori, G.B., eds. Modifying the risk for the smoker: proceedings of the third world conference on smoking and health, DHEW Pub. No. (NIH) 76-1221, New York: June 1975; Vol 1. U.S. Department of Health, Education, and Welfare, National Cancer Institute, pp. 441-449.

Brunnemann, K.D.; Adams, J.D.; Ho, D.P.; Hoffmann D. (1978) The influence of tobacco smoke on indoor atmospheres. II. Volatile and tobacco-specific nitrosamines in main and sidestream smoke and their contribution to indoor pollution: proceedings of the 4th joint conference on sensing of environmental pollutants. Washington, DC: American Chemical Society, pp. 876-880.

Buffler, P.A.; Pickle, L.W.; Mason, T.J.; Contant, C. (1984) The causes of lung cancer in Texas. In: Mizell, M.; Correa, P., eds. Lung cancer: causes and prevention. New York: Verlag Chemie International, pp. 83-99.

Burchfield, C.M.; Higgins, M.W.; Keller, J.B.; Howatt, W.F.; Butler, W.J.; Higgins, I.T.T. (1986) Passive smoking in childhood: respiratory conditions and pulmonary function in Tecumseh, Michigan. Am. Rev. Respir. Dis. 133:966-973.

25010320 76

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Burney, P.G.; Britton, J.R.; Chinn, S.; et al. (1987) Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study. Thorax 42:38-44.

Burrows, B.; Halonen, M.; Barbee, R.A.; Lebowitz, M.D. (1981) The relationship of serum immunoglobulin E to cigarette smoking. Am. Rev. Respir. Dis. 124:523-525.

Burrows, B.; Knudson, R.J.; Cline, M.G.; Lebowitz, M.D. (1988) A reexamination of risk factors for ventilatory impairment. Am. Rev. Respir. Dis. 138:829-836.

Burrows, B.; Martinez, F.D.; Halonen, M.; Barbee, R.A.; Cline, M.G. (1989) Association of asthma with serum IgE levels and skin-test reactivity to allergens. N. Engl. J. Med. 320:271-277.

Butler, T.L. (1988) The relationship of passive smoking to various health outcomes among Seventh-Day Adventists in California [dissertation]. Los Angeles: University of California at Los Angeles.

Butler, W.J. (1990) Unpublished comments submitted to EPA on its draft report entitled "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children," EPA/600/6-90/006A, May, 1990.

Butler, W.J. (1991) Supplementary information on confounding and the reported epidemiologic association between lung cancer and spousal smoking status (unpublished).

Caddeback, J.E.; Donovan, J.R.; Burg, W.R. (1976) Occupational aspects of passive smoking. Am. Ind. Hyg. Assoc. J. 37:263-267.

Cameron, P.; Kostin, J.S.; Oselett, B.; Stocker, R.; Tighe, G.; Winton, J.; Wolfe, J.H.; Zaks, J.M. (1969) The health of smokers' and nonsmokers' children. Journal of Allergy 43(6):336-341.

Camilli, A.E.; Burrows, B.; Knudson, R.J.; Lyle, S.K.; Lebowitz, M.D. (1987) Longitudinal changes in FEV1 in adults: effects of smoking and smoking cessation. Am. Rev. Respir. Dis. 135:794-799.

250103207

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Cano, J.P.; Catalin, J.; Badre, R.; Dumas, C.; Viala, A.; Guillerme, R. (1970) Determination de la nicotine par chromatographie en phase gazeuse. II. Applications. Ann. Pharm. Fr. 28:633-640.

CDC. *See* Centers for Disease Control.

Cederlof, R.; Friberg, L.; Hrubec, Z.; Lorich, U. (1975) The relationship of smoking and some social covariables in mortality and cancer morbidity: a ten year follow-up on a probability sample of 55,000 Swedish subjects age 18-69, Parts 1 and 2. Stockholm, Sweden: Department of Environmental Hygiene, Karolinska Institute.

Centers for Disease Control. (1989) Chronic disease reports: mortality trends—United States, 1979-1986. MMWR 38:189-191.

Centers for Disease Control. (1989) Years of potential life lost before age 65—United States, 1987. MMWR 38:27-28.

Centers for Disease Control. (1991a) Smoking-attributable mortality and years of potential life lost—United States, 1988. MMWR 40:62-71.

Centers for Disease Control. (1991b) Cigarette smoking among adults—United States, 1988. MMWR 40:757-765.

Chan, W.C.; Fung, S.C. (1982) Lung cancer in non-smokers in Hong Kong. In: Grundmann, E., ed. Cancer campaign, Vol. 6, cancer epidemiology. Stuttgart: Gustav Fischer Verlag, pp. 199-202.

Chan, W.C.; Colbourne, M.J.; Fung, S.C.; Ho, H.C. (1979) Bronchial cancer in Hong Kong, 1976-1977. Br. J. Cancer 39:182-192.

Chan, K.M.; Noble-Jamieson, C.M.; Elliman, A.; Bryan, E.M.; Silverman, M. (1989) Lung function in children of low birth weight. Arch. Dis. Child. 64:1284-1293.

250103078

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Chan, K.N.; Elliman, A.; Bryan, E.; Silverman, M. (1989) Respiratory symptoms in children of low birth weight. Arch. Dis. Child. 64:1294-1304.

Charlton, A. (1984) Children's coughs related to parental smoking. Brit. Med. J. 288:1647-1649.

Chen, M.F.; Kimisuka, G.; Wang, N.S. (1987) Human fetal lung changes associated with maternal smoking during pregnancy. Pediatr. Pulmonol. 3:51-58.

Chen, Y. (1989) Synergistic effect of passive smoking and artificial feeding on hospitalization for respiratory illness in early childhood. Chest 95:1004-1007.

Chen, Y.; Li, W. (1986) The effect of passive smoking on children's pulmonary function in Shanghai. Am. J. Public Health 76:515-518.

Chen, Y.; Li, W.; Yu, S. (1986) Influence of passive smoking on admissions for respiratory illness in early childhood. Br. Med. J. 293:303-306.

Chen, Y.; Li, W.; Yu, S.; Qian, W. (1988) Chang-Ning epidemiological study of children's health: I Passive smoking and children's respiratory diseases. Int. J. Epidemiol. 17:348-355.

Chilmonczyk, B.A.; Knight, G.J.; Palomaki, G.E.; Pulkkinen, A.J.; Williams, J.; Haddow, J.E. (1990) Environmental tobacco smoke exposure during infancy. Am. J. Public Health 80:1205-1208.

China Map Press. (1979) Atlas of Cancer Mortality in the People's Republic of China.

Clark, T.J.H.; Godfrey, S. (1983) Asthma. 2nd edition. Cambridge, _: Chapman and Hall Medical.

Claxton, L.D.; Morin, R.S.; Huges, T.J.; Lewtas, J. (1989) A genotoxic assessment of environmental tobacco smoke using bacterial bioassays. Mutat. Res. 222:81-99.

Coghlin, J.; Hammond, S.K.; Gann, P. (1989) Development of epidemiologic tools for measuring environmental tobacco smoke exposure. Am. J. Epidemiol. 130:696-704.

2501032079

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Cogswell, J.J.; Mitchel, E.B.; Alexander, J. (1987) Parental smoking, breast feeding, and respiratory infection in development of allergic diseases. Arch. Dis. Child. 62:336-344.

Colley, J.R.T. (1971) Respiratory disease in childhood. Br. Med. Bull. 27:9-14.

Colley, J.R.T. (1974) Respiratory symptoms in children and parental smoking and phlegm production. Br. Med. J. 2:201-204.

Colley, J.R.T.; Holland, W.W.; Corkhill, R.T. (1974) Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. Lancet 2:1031-1034.

Collier, A.M.; Goldstein, G.M.; Shrewsbury, R.P.; Zhang, C.A.; Williams, R.W. (1990) Urine cotinine elimination half-life in young children exposed to sidestream cigarette smoke. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 195-200.

Collins, M.H.; Moessinger, A.C.; Kleinerman, J.; Bassi, J.; Rosso, P.; Collins, A.M.; James, L.S.; Blanc, W.A. (1985) Fetal lung hypoplasia associated with maternal smoking: a morphometric analysis. Pediatr. Res. 19:408-412.

Comstock, G.W.; Meyer, M.B.; Helsing, K.J.; Tockman, M.S. (1981) The respiratory effects of household exposure to tobacco smoke and gas cooking. Am. Rev. Respir. Dis. 124:143-148.

Corbo, G.M.; Fuciarelli, F.; Foresi, A.; De Benedetto, F. (1989) Snoring in children: association with respiratory symptoms and passive smoking. Br. Med. J. 299:1491-1494.

Correa, P.; Fontham, E.; Pickle, L.; Lin, Y.; Haenszel, W. (1983) Passive smoking and lung cancer. Lancet 2:595-597.

Coultas, D.B.; Howard, C.A.; Peake, G.T.; Skipper, B.J.; Samet, J.M. (1987) Salivary cotinine levels and involuntary tobacco smoke exposure in children and adults in New Mexico. Am. Rev. Respir. Dis. 136:305-309.

250103208O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Coultas, D.B.; Howard, C.A.; et al. (1988) Discrepancies between self-reported and validated cigarette smoking in a community survey of New Mexico Hispanics. Am. Rev. Respir. Dis. 137:810-814.

Coultas, D.B.; Peake, G.T.; Samet, J.M. (1989) Questionaire assessment of lifetime and recent exposure to environmental tobacco smoke. Am. J. Epidemiol. 130:338-347.

Coultas, D.B.; Samet, J.M.; McCarthy, J.F.; Spengler, J.D. (1990a) A personal monitoring study to assess workplace exposure to environmental tobacco smoke. Am. J. Public Health 80:988-990.

Coultas, D.B.; Samet, J.M.; McCarthy, J.F.; Spengler, J.D. (1990b) Variability of measures of exposure to environmental tobacco smoke in the home. Am. Rev. Respir. Dis. 142:602-606.

Cummings, K.M. (1990) Statement to the U.S. Environmental Protection Agency Science Advisory Board Indoor Air Quality and Total Human Exposure Committee. Environmental Tobacco Smoke Review, December 4, 1990.

Cummings, K.M.; Markello, S.J.; Mahoney, M.C.; Marshall, J.R. (1989) Measurement of lifetime exposure to passive smoke. Am. J. Epidemiol. 130:122-132.

Cummings, K.M.; Markello, S.J.; et al. (1990) Measurement of current exposure to environmental tobacco smoke. Arch. Environ. Health 45:74-79.

Cutz, E.; Chan, W.; Track, N.S. (1981) Bombesin, calcitonin and leuenkephalin immunoreactivity in endocrine cells of the human lung. Experientia (Basel) 37:765-767.

Dagle, G.E.; McDonald, K.E.; Smith, L.G.; Stevens, D.L., Jr. (1978) Pulmonary carcinogenesis in rats given implants of cigarette smoke condensate in beeswax pellets. J. Natl. Cancer Inst. 61:905-910.

Dalager, N.A.; Pickle, L.W.; Mason, T.J.; Correa, P.; Fontham, E.; Stemhagen, A.; Buffler, P.A.; Ziegler, R.G.; Fraumeni, J.F. (1986) The relation of passive smoking to lung cancer. Cancer Res. 46:4808-4811.

2501032081

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Davies, R.F.; Day, T.D. (1969) A study of the comparative carcinogenicity of cigarette and cigar smoke condensate on mouse skin. Br. J. Cancer 23:363-368.

Day, N.E.; Brown, C.C. (1980) Multistage models and primary prevention of cancer. J. Natl. Cancer Inst. 64:977-989.

Dean, G.; Lee, P.N.; Todd, G.F.; Wicken, A.J. (1977) Report on a second retrospective study in North-east England. Part I. Factors related to mortality from lung cancer, bronchitis, heart disease and stroke in Cleveland County, with particular emphasis on the relative risks associated with smoking filter and plain cigarettes. Research Paper 14. London: Tobacco Research Council.

Deaner, R.M.; Trummer, M.J. (1970) Carcinoma of the lung in women. J. Thorac. Cardiovasc. Surg. 59:551-554.

DeMarini, D.M. (1983) Genotoxicity of tobacco smoke and tobacco smoke condensate. Mutat. Res. 114:59-89.

Dijkstra, L.; Houthuijs, D.; Brunekreef, B.; Akkerman, I.; Boleij, J.S.M. (1990) Respiratory health effects of the indoor environment in a population of Dutch children. Am. Rev. Respir. Dis. 142:1172-1178.

Dodge, R. (1982) The effects of indoor pollution on Arizona children. Arch. Environ. Health. 37:151-155.

Doll, R. (1971) The age distribution of cancer. Implication for models of carcinogenesis. J. R. Stat. Soc. A. 134:133-155.

Doll, R.; Hill, A.B. (1964a) Mortality in relation to smoking: ten years' observations of British doctors. Br. Med. J. i:1399-1410.

Doll, R.; Hill, A.B. (1964b) Mortality in relation to smoking: ten years' observations of British doctors. Br. Med. J. i:1460-1467.

05/15/92

2501032082

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Doll, R.; Peto, R. (1976) Mortality in relation to smoking: 20 years' observations on male British doctors. Br. Med. J. ii:1525-1536.

Doll, R.; Peto, R. (1978) Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J. Epidemiol. Community Health 32:303-313.

Doll, R.; Hill, A.B.; Kreyberg, L. (1957) The significance of cell type in relation to the aetiology of lung cancer. Br. J. Cancer 11:43-48.

Doll, R.; Gray, R.; Hafner, B.; Peto, R. (1980) Mortality in relation to smoking: 22 years' observations on female British doctors. Br. Med. J. i:967-971.

Dontenwill, W.; Chevalier, H.J.; Harke, H.P.; Lafrenz, U.; Reckzeh, G.; Schneider, B. (1973) Investigations on the effects of chronic cigarette smoke inhalation in Syrian golden hamsters. J. Natl. Cancer Inst. 51:1781-1832.

Dube, M.F.; Green, C.R. (1982) Methods of collection of smoke for analytical purposes. Recent Adv. Tobacco Sci. 8:42-102.

Dupont, W.D.; Plummer, W.D. (1990) Power and sample size calculations: a review and computer program. In: Controlled Clinical Trials, Vol. 11, Elsevier Science Publishing Co., New York, pp. 116-128.

Dutau, G.; Enjaume, C.; Petrus, M.; Darcos, P.; Demeurisse, P.; Rochiccioli, P. (1981) Enquete epidemiologue sur le tabagisme passif des enfants de 0 a 6 ans. Arch. Fr. Pediatr. 38:721-725.

Eatough, D.J.; Benner, C.; Mooney, R.L.; Batholomew, D.; Steiner, D.S.; Hansen, L.D.; Lamb, J.D.; Lewis, E.A. (1986) Gas and particle phase nicotine in environmental tobacco smoke: proceedings of 79th annual meeting of the Air Pollution Control Association, Paper 86-68.5. June 22-27, 1986; Minneapolis, MN.

2501032083

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Eatough, D.J.; Benner, C.L.; Bayona, J.M.; Caka, H.; Tang, H.; Lewis, L.; Lamb, J.D.; Lee, M.L.; Lewis, E.A.; Hansen, L.D. (1989a) Measurement of toxic and related air pollutants. Pittsburgh, PA: Air Pollution Control Association, pp. 132-139.

Eatough, D.J.; Benner, C.L.; Tang, H.; Landon, V.; Richards, G.; Caka, F.M.; Crawford, F.; Lewis, E.A.; Hansen, L.D.; Eatough, N.L. (1989b) The chemical composition of environmental tobacco smoke. III. Identification of conservative tracers of environmental tobacco smoke. Environ. Int. 15:19-28.

Eatough, D.J.; Caka, F.M.; Crawford, J.; Braithwaite, S.; Hansen, L.D.; Lewis, E.A. (1990) Environmental tobacco smoke in commercial aircraft. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2. Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 311-316.

Ekwo, E.; Weinberger, W.M.; Lachenbruch, P.A.; Humtley, W.H. (1983) Relationship of parental smoking and gas cooking to respiratory disease in children. Chest 84:662-668.

Elliot, L.P.; Rowe, D.R. (1975) Air quality during public gatherings. J. Air Pollut. Control Assoc. 25:635-636.

Etzel, R.A.; Greenberg, R.A.; Haley, N.J.; Loda, F.A. (1985) Urinary cotinine excretion in neonates exposed to tobacco smoke products in utero. J. Pediatr. 107:146-148.

Eudy, L.W.; Thorne, F.A.; Heavor, D.L.; Green, C.R.; Ingebrethsen, B.J. (1985) Studies on the vapour-phase distribution of environmental nicotine by selected trapping and detection methods. Presented at: 39th Tobacco Chemists Research Conference; October; Montreal.

Eudy, L.W.; Thomas, F.A.; Heavner, D.L.; Green, C.R.; Ingebrethsen, B.J. (1986) Studies on the vapor-particulate phase distribution of environmental nicotine by selective trapping and detection methods: proceedings of the Air Pollution Control Association 79th annual meeting, June 22-27, pp. 2-14.

2501032084 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Evans, D.; Levison, J.; Feldman, C.H.; et al. (1987) The impact of passive smoking on emergency room visits of urban children with asthma. Am. Rev. Respir. Dis. 135:567-572.

Evans, R.; Mullolly, D.I.; Wilson, R.W.; Gergen, P.J., Rosenberg, H.M.; Grauman, T.S.; Chevarley, F.M.;

Feinlein, M. (1987) National trends in the morbilidity and mortality of asthma in the U.S. Chest 91(6):655-745.

Fergusson, D.M.; Horwood L.J.; Shannon, F.T.; Taylor, B. (1981) Paternal smoking and lower respiratory illness in the first three years of life. J. Epidemiol. Community Health 35:180-184.

Ferris, B.G.; Ware, J.H.; Berkey, C.S.; Dockery, D.W.; Spiro, A.; Speizer, F.E. (1985) Effects of passive smoking on health of children. Environ. Health Perspect. 62:289-295.

Feyerabend, C.; Higenbottam, T.; Russell, M.A.H. (1982) Nicotinic concentrations in urine and saliva of smokers and nonsmokers. Brit Med J 284:1002-04.

Fielding, J.E. (1985) Smoking: health effects and control (Part I). N. Engl. J. Med. 313:491.

Fiore, M.C.; Novotny, T.E.; Pierce, J.P.; Hatziandreu, E.J.; Patel, K.M.; Davis, R.M. (1989) Trend in cigarette smoking in the United States. The changing influence of gender and race. JAMA 261:49-55.

First, M.W. (1984) Environmental tobacco smoke measurements: retrospect and prospect. Eur. J. Respir. Dis. 65 (Suppl. 133):9-16.

Fleming, D.W.; Cochi, S.L.; Hightower, A.W.; Broome, C.V. (1987) Childhood upper respiratory tract infections: to what degree is incidence affected by day-care attendance? Pediatrics 79:55-60.

Floderus, B.; Cederlof, R.; Friberg, L. (1988) Smoking and mortality: a 21-year follow-up based on the Swedish Twin Registry. Int. J. Epidemiol. 17(2):322.

05/15/92

2501032085

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Fontham, E.T.H.; Correa, P.; Wu-Williams, A.; Reynolds, P.; Greenberg, R.S.; Buffler, P.A.; Chen, V.W.; Boyd, P.; Alterman, T.; Austin, D.F.; Liff, J.; Greenberg, S.D. (November 1991) Lung cancer in nonsmoking women: a multicenter case-control study. Cancer Epidemiol. Biomarkers and Prev., Vol. 1:1, pp. 35-44.

Fraser, G.E.; Beeson, W.L., and Phillips, R.L. (1991) Diet and lung cancer in California Seventh Day Adventists. Am J Epidemiol 133:683-93.

Freedman, D.A.; Navidi, W. (1987a) On the multistage model for carcinogenesis. Tech. Report. No. 47, University of California.

Freedman, D.A.; Navidi, W. (1987b) On the risk of lung cancer for ex-smokers. Tech. Report. No. 135, University of California.

Friedman, G.D.; Petitti, D.B.; Bawol, R.D. (1983) Prevalence and correlates of passive smoking. Am. J. Public Health 73:401-_____.

Gaffney, M.; Altshuler, B. (1988) Examination of the role of cigarette smoke in lung carcinogenesis using multistage models. J. Natl. Cancer Inst. 80:925-931.

Gairola, C. (1982) Genetic effects of fresh cigarette smoke in Saccharomyces cerevisiae. Mutat. Res. 102:123-136.

Gao, Y.; Blot, W.J.; Zheng, W.; Ershow, A.G.; Hsu, C.W.; Levin, L.I.; Zhang, R.; Fraumeni, J.F. (1987) Lung cancer among Chinese women. Intl. J. Cancer 40:604-609.

Garfinkel, L. (1981) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J. Natl. Cancer Inst. 6:1061-1066.

Garfinkel, L. (1984) Passive smoking and cancer: American experience. Prev. Med. 13:691-697.

Garfinkel, L.; Silverberg, E. (1991) Lung cancer and smoking trends in the United States over the past 25 years. CA 41:137-145.

2501032086 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Garfinkel, L.; Stellman, S.D. (1988) Smoking and lung cancer in women: findings in a prospective study. Cancer Res. 48:6951-6955.

Garfinkel, L. (1985) Selection, follow-up, and analysis in the American Cancer Society Prospective Studies. Presented at a workshop on the selection, follow-up, and analysis in prospective studies held at the Waldorf-Astoria Hotel, October 3-5, 1983; New York.

Garfinkel, L.; Auerbach, O.; Joubert, L. (1985) Involuntary smoking and lung cancer: a case-control study. J. Natl. Cancer Inst. 75:463-469.

Geller-Bernstein, B.; Kenett, R.; Weisglass, L.; Tsur, S.; Lahav, M.; Levin, S. (1987) Atopic babies with wheezy bronchitis. Allergy 42:85-91.

Geng, G.; Liang, Z.H.; Zhang, G.L. (1988) On the relationship between smoking and female lung cancer. Smoking and Health, Elsevier Science Publishers, pp. 483-486.

Geng, G.; Liang, Z-H; et al. Effects of smoking and passive smoking on female lung cancer in Tianjin area. Tianjin, People's Republic of China: Dept. of Epidemiol., Tianjin Med. Col.

Gerrard, J.W.; Helner, D.C.; Ko, C.G.; Mink, J.; Meyers, A.; Dosman, J.A. (1980) Immunoglobulin levels in smokers and non-smokers. Ann. Allergy 44:261-262.

Gillis, C.R.; Hole, D.J.; Hawthorne, V.M.; Boyle, P. (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur. J. Respir. Dis. 133(Suppl.):121-126.

Glantz, S.A.; Parmley, W.W. (1991) Passive smoking and heart disease. Circulation 83:1-12.

Goldstein, G.M.; Collier, A.; Etzel, R.; Lewtas, J.; Haley, N. (1987) Elimination of urinary cotinine in children exposed to known levels of side-stream cigarette smoke. In: Seifert, H.; Esdorn, M.; Fischer, H.; Ruden, J.; Wegner, eds. Indoor air '87, Vol. 2, B. Berlin: Oraniendruck GmbH, pp. 61-67.

2501032087

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Gortmaker, S.L.; Walker, D.K.; Jacobs, F.H.; Ruch-Ross, H. (1982) Parental smoking and the risk of childhood asthma. Am. J. Pub Health 72:572-579.

Graham, N.M.H.; Woodward, A.J.; Ryan, P.; Douglas, R.M. (1990) Acute respiratory illness in Adelaide children. II: The relationship of maternal stress, social supports and family functioning. Int. J. Epidemiol. 19:937-944.

Greenberg, R.A.; Haley, N.J.; Etzel, R.A.; Loda, F.A. (1984) Measuring the exposure of infants to tobacco smoke. N. Engl. J. Med. 310:1075-1078.

Greenberg, R.A.; Bauman, K.E.; Glover, L.H.; Strechar, V.J.; Kleinbaum, D.G.; Haley, N.J.; Stedman, H.C.; Fowler, M.G.; Loda, F.A. (1989) Ecology of passive smoking by young infants. J. Pediatr. 114:774-780.

Greenberg, R.A.; Bauman, K.E.; Strecher, V.J.; Keyes, L.L.; Glover, L.H.; Haley, N.J.; Stedman, H.C.; Loda, F.A. (1991) Passive smoking during the first year of life. Am. J. Public Health 81:850-853.

Greenland, S. (1987) Quantitative methods in the review of epidemiologic literature. Epidem Rev 9:1-30.

Grimmer, G.; Brune, H.; Dettbarn, G.; Naujack, K.-W.; Mohr, U.; Wenzel-Hartung, R. (1988) Contribution of polycyclic aromatic compounds to the carcinogenicity of sidestream smoke of cigarettes evaluated by implantation into the lungs of rats. Cancer Lett. 43:173-177.

Guerin, M. (1987) Formation and physicochemical nature of sidestream smoke. In: O'Neill, I.K.; Brunnemann, K.D.; Dodet, B.; Hoffmann, D., eds. Environmental carcinogens—selected methods of analysis, v. 9, passive smoking. IARC Monographs No. 81. Lyon, France: International Agency for Research on Cancer.

Guerin, M.R.; Jenkins, R.A.; Tomkins, B.A. (1992) The chemistry of environmental tobacco smoke: Composition and measurement. Lewis Publishers, Chelsea, MI.

2501032088

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Gwinn, J.V.; Martinez, F.D.; Wright, A.L.; Ray, C.G.; Taussig, L.M. (1991) Etiology and symptomatology of lower respiratory illnesses (LRIs) in the first three years of life. Am. Rev. Respir. Dis. 143:A509.

Haddow, J.E.; Palomaki, G.E.; Knight, G.J. (1986) Use of serum cotinine to assess the accuracy of self-reported non-smoking. Br. Med. J. 293:1306.

Haddow, J.E.; Knight, G.J.; et al. (1987) Cigarette consumption and serum cotinine in relation to birthweight. Br. J. Obstet. Gynaecol. 94:678-681.

Haddow, J.E.; Knight, G.J.; Palomaki, G.E.; et al. (1988) Second-trimester serum cotinine levels in nonsmokers in relation to birth weight. Am. J. Obstet. Gynecol. 159:481-484.

Haenszel, W.; Taeuber, K.E. (1964) Lung-cancer mortality as related to residence and smoking histories. II. White females. J. Natl. Cancer Inst. 32:803-838.

Haglund, B.; Cnattingius, S. (1990) Cigarette smoking as a risk factor for sudden infant death syndrome: a population-based study. Am. J. Public Health 80:29-32.

Haley, N.J.; Colosimo, S.G.; Axelrad, C.M.; Harris, R.; Sepkovic, D.W. (1989) Biochemical validation of self-reported exposure to environmental tobacco smoke. Environ. Res. 49:127-135.

Halonen, M.; Barbee, R.A.; Lebowitz, M.D.; Burrows, B. (1982) An epidemiologic study of the interrelationships of total serum immunoglobulin E, allergy skin-test reactivity, and eosinophilia. J. Allergy Clin. Immunol. 69:221-228.

Halonen, M.; Stern, D.; Lyle, S.; Wright, A.; Taussig, L.; Martinez, F.D. (1991) Relationship of total serum IgE levels in cord and 9-month sera of infants. Clin. Exp. Allergy 21:235-241.

Hammond, E.C. (1966) Smoking in relation to the death rates of one million men and women. In: Haenszel, W., ed. Epidemiological approaches to the study of cancer and other chronic diseases. National Cancer Institute Monograph No. 19, Washington, DC: pp. 127-204.

2501032089 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Hammond, E.C.; Horn, D. (1958a) Smoking and death rates: report on forty-four months of follow-up of 187,783 men. I. Total mortality. JAMA 166:1159-1172.

Hammond, E.C.; Horn, D. (1958b) Smoking and death rates: report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. JAMA 166:1294-1308.

Hammond, S.K.; Leaderer, B.P. (1987) A diffusion monitor to measure exposure to passive smoking. Environ. Sci. and Technol. 21:494-497.

Hammond, E.C.; Seidman, H. (1980) Smoking and cancer in the United States. Prev. Med. 9:169-173.

Hammond, E.C.; Selikoff, I.J. (1981) Commentary: passive smoking and lung cancer with comments on two new papers. Environ. Res. 24:444-452.

Hammond, S.K.; Leaderer, B.P.; Roche, A.C.; Schenker, M. (1987) Collection and analysis of nicotine as a marker for environmental tobacco smoke. Atmos. Environ. 21:457-462.

Hammond, S.K.; Smith, T.J.; Woskie, S.R.; Leaderer, B.P.; Bettinger, N. (1988) Markers of exposure to diesel exhaust and cigarette smoke in railroad workers. Am. Ind. Hyg. Assoc. J. 49:516-522.

Hammond, S.K.; Lewtas, J.; Mumford, J.; Henderson, J.; Henderson, F.W. (1989) Exposures to environmental tobacco smoke in homes. In: Measurement of toxic and related air pollutants, Environmental Protection Agency/Air and Waste Management Association international symposium, Pittsburgh, PA: Air and Waste Management Association, pp. 590-595.

Hammond, S.K.; Gann, P.H.; Coughlin, J.; Tannenbaum, S.R.; Skipper, P.L. (1990) Tobacco smoke exposure and carcinogen-hemoglobin adducts. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air, Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 157-161.

250103209

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Hanbury, W.J. (1964) Bronchogenic carcinoma in women. Thorax 19:338-342.

Hanrahan, J.P.; Tager, I.B.; Segal, M.R.; et al. (1990) Effect of prenatal smoking on infant lung function. Am. Rev. Respir. Dis. 141:A282.

Hanson, B.; McGue, M.; Roitman-Johnson, B.; Segal, N.L.; Bouchard, T.J.; Blumenthal, M.N. (1991) Atopic disease and immunoglobulin E in twins reared apart and together. Am. J. Hum. Genet. 48:873-879.

Harmsen, H.; Effenberger, E. (1957) Tobacco smoke in public transportation, dwellings and work rooms. Arch. Hug. 141:383-400.

Hasselblad, V.; Humble, C.G.; Graham, M.G.; Anderson, H. (1981) Indoor environmental determinants of lung function in children. Am. Rev. Respir. Dis. 123:479-485.

Hawthorne, A.R.; Gammage, D.; Dudney, C.S.; Hingerty, B.E.; Schuresko, D.D.; Parzyek, D.C.; Womak, D.R.; Morris, S.A.; Westeley, R.R.; White, D.A.; Schrimscher, J.M. (1984) Air indoor quality study of forty east Tennessee homes. ORNL 5965. Oak Ridge, TN: Oak Ridge National Laboratory, pp. 134.

Hawthorne, V.M.; Fry, J.S. (1978) Smoking and health: the association between smoking behaviour, total mortality and cardiorespiratory disease in West Central Scotland. J. Epidemiol. Community Health 32:260-266.

Higgins, C.E. (1987) Organic vapor phase composition of sidestream and environmental tobacco smoke from cigarettes: Proceedings of the Environmental Protection Agency/Air Pollution Control Association symposium on measurement of toxic and related air pollutants, pp. 140-151.

Hill, A.B. (1953) Observation and experiment. N. Engl. J. Med. 248:995-1001.

Hill, A.B. (1965) The environment and disease: association or causation? proceedings of the Royal Society of Medicine 58:295-300.

25010320 91

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Hinds, W.C.; First, M.W. (1975) Concentrations of nicotine and tobacco smoke in public places. N. Engl. J. Med. 292:844-845.

Hinton, A.E. (1989) Surgery for otitis media with effusion in children and its relationship to parental smoking. J. Laryngol. Otol. 103:559-561.

Hirayama, T. (1967) Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo: National Cancer Center Research Institute.

Hirayama, T. (1975a) Smoking and cancer: a prospective study on cancer epidemiology based on a census population in Japan. In: Steinfeld, J.; Griffiths, W.; Ball, K.; et al., eds. Proceedings of the 3rd world conference on smoking and health, Vol. II, Washington, DC: U.S. Department of Health, Education, and Welfare, pp. 65-72.

Hirayama, T. (1975b) Prospective studies on cancer epidemiology based on a census population in Japan. In: Bucalossi, P.; Veronesi, U.; Cascinelli, N., eds. Proceedings of the XIth international cancer congress, Florence, Italy, 1974, Vol. 3, Cancer epidemiology, environmental factors. Amsterdam: Excerpta Medica, pp. 26-35.

Hirayama, T. (1977) Epidemiology of lung cancer based on population studies. In: National Cancer Center Library, ed. Collected papers from the National Cancer Center Research Institute, Vol. 12. Tokyo: National Cancer Center, pp. 452-461.

Hirayama, T. (1978) Prospective studies on cancer epidemiology based on census population in Japan. In: Nieburgs, H.E., ed. Prevention and detection of cancer, Vol. 1, Etiology. New York: Marcel Dekker, pp. 1139-1147.

Hirayama, T. (1981a) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br. Med. J. 282:183-185.

Hirayama, T. (1981b) [Letter] Br. Med. J. 283:916-917.

Hirayama, T. (1982) Smoking and cancer in Japan. A prospective study on cancer epidemiology based on census population in Japan. Results of 13 years follow up. In: Tominaga, S.; Aoki,

2501032092

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

K., eds. The UICC smoking control workshop, Nagoya, Japan, August 24-25, 1981. Nagoya: University of Nagoya Press, pp. 2-8.

Hirayama, T. (1983a) Passive smoking and lung cancer: consistency of association. Lancet 2:1425-1426.

Hirayama, T. (1983b) Passive smoking and lung cancer. Presented at the 5th world conference on smoking and health, Winnipeg, Canada.

Hirayama, T. (1984) Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev. Med. 13:680-690.

Hirayama, T. (1985) A cohort study on cancer in Japan. In: Blot, W.J.; Hirayama, T.; Hoel, D.G., eds. Statistical methods in cancer epidemiology. Hiroshima: Radiation Effects Research Foundation, pp. 73-91.

Hirayama, T. (1988) Duration of exposure as a determinant of lung cancer risk in passive smokers. Environ. Tech. L. 9:731-732.

Hirayama, T. (1989) Dietary habits are of limited importance in influencing the lung cancer risk among Japanese females who never smoked. In: Bieva, D.J.; Courtois, Y.; Govaerts, M., eds. Present and future of indoor air quality. New York: Elsevier.

Hirayama, T. (1990) Passive smoking and cancer: the association between husbands' smoking and cancer in the lung of non-smoking wives. In: Kaskuga, H., ed. _____ Berlin: Springer-Verlag.

Hoegg, U.R. (1972) Cigarette smoke in closed spaces. Environ. Health Perspect. 2:117-128.

Hoffman, H.J.; Damus, K.; Hillman, L.; Krongrad, E. (1988) Risk factors for SIDS. Results of the National Institute of Child Health and Human Development SIDS Cooperative Epidemiological Study. Ann. N.Y. Acad. Sci. 533:13-30.

2501032093

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Hoffmann, D.; Hecht, S.S. (1989) Advances in tobacco carcinogenesis. In: Springer handbook of experimental pharmacology: chemical carcinogenesis and mutagenesis (in press).

Hoffmann, D.; Wynder, E.L. (1971) A study of tobacco carcinogenesis. XI. Tumor initiators, tumor accelerators, and tumor promoting activity of condensate fractions. Cancer 27:848-864.

Hoffmann, D.; Haley, N.J.; Adams, J.D.; Brunnemann, K.D. (1984) Tobacco sidestream smoke. Uptake by nonsmokers. Prev. Med. 13:608-617.

Hoffmann, D.; Brunnemann, K.D.; Haley, N.J. (1989) Absorption of smoke constituents by nonsmokers. In: Reducing workplace exposures to environmental tobacco smoke. EPA/HHS Manual.

Hole, D.J; Gillis, C.R.; Chopra, C.; Hawthorne, V.M. (1989) Passive smoking and cardiorespiratory health in a general population in the west of Scotland. Br. Med. J. 299:423-427.

Hopp, R.J.; Bewtra, A.; Nair, N.M.; Townley, R.G. (1985) The effect of age on methacholine response. J. Allergy Clin. Immunol. 76:609-613.

Hopp, R.J.; Townlwy, R.G.; Biven, R.E.; Bewtra, A.K.; Nair, N.M. (1990) The presence of airway reactivity before the development of asthma. Am. Rev. Respir. Dis. 141:2-8.

Hoppenbrouwers, T.; Ceeb, M.; Arakawa, K.; Hodgman, J.E. (1981) Seasonal relationship of sudden infant death syndrome and environmental pollutants. Am. J. Epidemiol. 113:623-635.

Hornon, E.R. (ed) Almanac of the 50 States. Information Publications, Palo Alto, California.

Horwood, L.J.; Fergusson, D.M.; Shannon, F.T. (1985) Social and familial factors in the development of early chilhood asthma. Pediatrics 75:859-868.

2501032094

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Humble, C.G.; Samat, J.M.; Pathak, D.R.; Skipper, B.J. (1985) Cigarette smoking and lung cancer in 'Hispanic' whites and other whites in New Mexico. Am J Public Health 75:145-8.

Humble, C.G.; Samet, J.M.; Pathak, D.R. (1987) Marriage to a smoker and lung cancer risk. Am. J. Public Health 77:598-602.

Husgafvel-Pursiainen, K.; Sorsa, M.; Moller, M.; Benestad, C. (1986) Genotoxicity and polynuclear aromatic hydrocarbon analysis of environmental tobacco smoke samples from restaurants. Mutagenesis 1:287-291.

IARC. *See* International Agency for Research on Cancer.

Idle, J.R. (1990) Titrating exposure to tobacco smoke using cotinine--a minefield of misunderstandings. J. Clin. Epidemiol. 43:313-317.

Inoue, R.; Hirayama, T. (1988) Passive smoking and lung cancer in women. In: Smoking and health. Elsevier Science Publishers, pp. 283-285.

International Agency for Research on Cancer. (1986) IARC monographs on the evaluation of the carcinogenic risk of chemicals to man. Vol. 38. Tobacco smoking. Lyon, France: World Health Organization.

International Agency for Research on Cancer. (1987) Environmental carcinogens—methods of analysis and exposure measurement. Vol. 9: Passive smoking. O'Neill, I.K.; Brunnemann, K.D.; Dodet, B.; Hoffmann, D. eds. Lyon, France: IARC Scientific Publications No. 81.

Ishizu, Y. (1980) General equation or the estimation of indoor pollution. Environ. Sci. Technol. 14:1254-1257.

Iversen, M.; Birch, L.; Lundqvist, G.R.; Elbrond, O. (1985) Middle ear effusion and the indoor environment. Arch. Environ. Health 40:74-79.

Janerich, D.T.; Thompson, W.D.; Varela, L.R.; et al. (1990) Lung cancer and exposure to tobacco smoke in the household. N. Engl. J. Med. 323:632-636.

2501032095

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Jarvis, M.J. (1987) Uptake of environmental tobacco smoke. IARC Sci. Publ. 81:43-58.

Jarvis, M.J. (1989) Application of biochemical intake markers to passive smoking measurement and risk estimation. Mutat. Res. 222:101-110.

Jarvis, M.J.; Russell, M.H.; Feyerabend, C. (1983) Absorption of nicotine and carbon dioxide from passive smoking under natural conditions of exposure. Thorax 38:829-833.

Jarvis, M.; Tunstall-Pedoe, H.; Feyerabend, C.; Vesey, C.; Kabat, G.C.; Wynder, E.L. (1984) Lung cancer in nonsmokers. Cancer 53:1214-1221.

Jarvis, M.J.; Russell, M.A.H.; Feyerabend, C.; Eiser, J.R.; Morgan, M.; Gammage, P.; Gray, E.M. (1985) Passive exposure to tobacco smoke: saliva cotinine concentrations in a representative sample of non-smoking children. Br. Med. J. 291:927-929.

Joly, O.G.; Lubin, J.H.; Caraballoso, M. (1983) Dark tobacco and lung cancer in Cuba. J. Natl. Cancer Inst. 70:1033-1039.

Kabat, G.C. (1990) Epidemiologic studies of the relationship between passive smoking and lung cancer. Presented at the 1990 annual winter meeting of the Toxicology Forum in Washington, DC.

Kabat, G.C.; Wynder, E.L. (1984) Lung cancer in nonsmokers. Cancer 53:1214-1221.

Kabat, G.C.; Wynder, E.L. (1984) Lung cancer in nonsmokers. Cancer 53:1214-1221.

Kahn, H.A. (1966) The Dorn study of smoking and mortality among U.S. veterans: report on eight and one-half years of observation. In: Haenszel, W., ed. Epidemiological approaches to the study of cancer and other chronic diseases. National Cancer Institute Monograph No. 19, Washington, DC, pp. 1-125.

Kalandidi, A.; Trichopoulos, D.; Hatzakis, A.; Tzannes, S.; Saracci, R. (1987) Passive smoking and chronic obstructive lung disease. Lancet ii:1325-1326.

2501032096

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Kalandidi, A; Katsouyanni, K.; Voropoulou, N.; et al. (1990) Passive smoking and diet in the etiology of lung cancer among non-smokers. Cancer Causes and Control 1:15-21.

Kaplan, H.S.; Tsuchitani, P.J. (eds) (1978) Cancer in China, Alan R. Liss, Inc., New York, 1978.

Kasuga, H.; Hasebe, A.; Osaka, F.; Matuski, H. (1979) Respiratory symptoms in school children and the role of passive smoking. Tokai J. Exp. Clin. Med. 4:101-104.

Katada, H.; Mikami, R.; Konishi, M.; Koyama, Y.; Narita, N. (1988) Effect of passive smoking in lung cancer development in women in the Nara region. Gan No Rinsho 34(1):21-27.

Katsouyanni, K.; Kogevinas, M.; Dontas, N.; Maisonneuve, P.; Boyle, P.; Trichopoulos, D. (1990) Mortality from malignant neoplasms in Greece 1960-1985. Greek Cancer Society, Athens, pp. 1-125 [in Greek].

Katz, D.; Baptista, J.; Azen, S.P.; Pike, M.C. Obtaining confidence intervals for the risk ratio in cohort studies. Biometrics 78:469-474.

Kauffmann, F.; Tessier, J.F.; Oriol, P. (1983) Adult passive smoking in the home environment: a risk factor for chronic airflow limitation. Am. J. Epidemiol. 117:269-280.

Kauffmann, F.; Neukirch, F.; Orobaeff, M.; Marne, M.J.; Claud, J.R.; Lellouch, J. (1986) Eosinophils, smoking, and lung function. An epidemiologic survey among 912 working men. Am. Rev. Respir. Dis. 134:1172-1175.

Kauffmann, F.; Dockery, D.W.; Speizer, F.E.; Ferris, B.G. (1989a) Respiratory symptoms and lung function in relation to passive smoking: a comparative study of American and French Women. Int. J. Epidemiol. 18:334-344.

Kauffmann, F.; Tager, I.B.; Munoz, A.; Speizer, F.E. (1989b) Familial factors related to lung function in children aged 6-10 years: results from the PAARC epidemiologic study. Am. J. Epidemiol. 129:1289-1299.

250103097

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Kentner, M.; Triebig, G.; Weltle, D. (1984) The influence of passive smoking on pulmonary function: a study of 1351 office workers. Prev. Med. 13:656-69.

Kleinbaum, D.G.; Kupper, L.L.; Morgenstern, H. Epidemiologic Research, Lifetime Learning Publications, Belmont, California, 1982.

Knoth, A.; Bohn, H.; Schmidt, F. (1983) Passive smoking as a causal factor of bronchial carcinoma in female nonsmokers. Med. Klin. 78:66-69.

Koo, L.C. (1988) Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. Nutr. Cancer 11:155-172.

Koo, L.C. (1989) Environmental tobacco smoke and lung cancer: is it the smoke or the diet? Elsevier Science Publishers.

Koo, L.C.; Ho, J.H-C.; Saw, D. (1983) Active and passive smoking among female lung cancer patients in Hong Kong. J. Exp. Clin. Cancer Res. 4:367-375.

Koo, L.C.; Ho, J.H-C.; Saw, D. (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? J. Exp. Clin. Cancer Res. 3:277-283.

Koo, L.C.; Ho, J.H-C.; Lee, N. (1985) An analysis of some risk factors for lung cancer in Hong Kong. Int. J. Cancer 35:149-155.

Koo, L.C., Ho, J.H.; Saw, D.; Ho, C.Y. (1987) Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. Int J Cancer 39:162-169.

Koo, L.C.; Ho, J. H-C.; Rylander, R. (1988b) Life-history correlates of environmental tobacco smoke: a study on nonsmoking Hong Kong Chinese wives with smoking versus nonsmoking husbands. Soc. Sci. Med. 26(7):751-760.

Koutrakis, P.; Fasano, A.M.; Slater, J.L.; Spengler, J.D.; McCarthy, J.F.; Leaderer, B.P. (1989) Atmos. Environ. 23:2767-2773.

2501032098

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Kraemer, M.J.; Richardson, M.A.; Weiss, N.S.; et al. (1983) Risk factors for persistent middle-ear effusions: otitis media, cattarah, cigarette smoke exposure, and atopy. JAMA 249:1022-1025.

Krall, E.A.; Valadian, I.; Dwyer, J.T.; Gardner, J. (1989) Accuracy of recalled smoking data. Am J Publ Health 79:200.

Krzyzanowski, M.; Quackenboss, J.J.; Lebowitz, M.D. (1990) Chronic respiratory effects of indoor formaldehyde exposure. Environ. Res. 52:117-125.

Kuller, L.H.; Garfinkel, L.; Correa, P.; Haley, N.; Hoffmann, D.; Preston-Martin, S.; Sandler, D. (1986) Contribution of passive smoking to respiratory cancer. Environ. Health Perspect. 70:57-69.

Kurihara, M.; Aoki, K.; Miller, R.W.; Muir, C.S. (eds) Changing Cancer Patterns and Topics in Cancer Epidemiology, Plenum Press, New York, 1989.

Lam, W.K. (1985) A clinical and epidemiological study of carcinoma of lung in Hong Kong [doctoral thesis]. Hong Kong: University of Hong Kong.

Lam, T. H.; Kung, I.T.M.; Wong, C.M.; Lam, W.K.; Kleevens, J.W.L.; Saw, D.; Hsu, C.; Seneviratne, S.; Lam, S.Y.; Lo, K.K.; Chan, W.C. (1987) Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. Br. J. Cancer 6:673-678.

Layard, M.W.; Viren, J.R. (1989) Assessing the validity of a Japanese cohort study. Elsevier Science Publishers B.V. (Biomedical Division).

Leaderer, B.P. (1988) Measuring exposure to environmental tobacco smoke. Report prepared for the U. S. Environmental Protection Agency.

Leaderer, B.P. (1989) Unpublished data.

Leaderer, B. (1990) Assessing exposure to environmental tobacco smoke. Risk Anal. 10(1):19-26.

2501032099

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Leaderer, B.P.; Hammond, S.K. (1991) Evaluation of vapor-phase nicotine and respirable suspended particle mass as markers for environmental tobacco smoke. Environ. Sci. Technol. 25(4):770-777.

Leaderer, B.P.; Cain, W.S.; Isseroff, R.; Berglund, L.G. (1984) Ventilation requirements in buildings II. Particulate matter and carbon monoxide from cigarette smoking. Atmos. Environ. 18:99-106.

Leaderer, B.P.; Koutrakis, P.; Briggs, S.; Rizzuto, J. (1990) Impact of indoor sources on residential and concentrations. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 269-274.

Lebowitz, M.D. (1984) The effects of environmental tobacco smoke exposure and gas stoves on daily peak flow rates in asthmatic and non-asthmatic families. Eur. J. Respir. Dig. 133:190-195.

Lebowitz, M.D.; Burrows, B. (1976) Respiratory symptoms related to smoking habits of family adults. Chest 69:49-50.

Lebowitz, M.D.; Holberg, C.J. (1988) Effects of parental smoking and other risk factors on the development of pulmonary function in children and adolescents. Analysis of two longitudinal population studies. Am. J. Epidemiol. 128:589-597.

Lebowitz, M.D.; Holberg, C.J.; Knudson, R.J.; Burrows, B. (1987) Longitudinal study of pulmonary function development in childhood, adolescence, and early adulthood. Am. Rev. Respir. Dis. 136:69-75.

Lebowitz, M.D.; Quackenboss, J.J. (1990) The effect of environmental tobacco smoke on pulmonary function. Int. Arch. Occup. Environ. Health (Suppl):147-152.

Lebret, E.; Boley, J.; Brumekreef, B. (1990) Environmental tobacco smoke in Dutch homes. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and

2501032100

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

climate, July 29-August 3. Vol. 2: Characteristics of indoor air, Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 263-268.

Lee, P.N. (1986) Does breathing other people's tobacco smoke cause lung cancer? [Letter] Br. Med. J. 293:1503-1504.

Lee, P.N. (1987a) Lung cancer and passive smoking: association an artifact due to misclassification of smoking habits. Toxicol. Lett. 35:157-162.

Lee, P.N. (1987b) Passive smoking and lung cancer association: a result of bias? Hum. Toxicol. 6:517-524.

Lee, P.N. (1988) Misclassification of smoking habits and passive smoking. Berlin: Springer.

Lee, P.N. (1989) Passive smoking and lung cancer: fact or fiction. In: Bieva, C.J.; Courtois, Y.; Govaerts, M., eds. Present and Future of Indoor Air Quality, Excerpta Medica, Amsterdam, pp. 119-128.

Lee, P.N. (1990) A detailed review of epidemiological evidence relating environmental tobacco smoke (ETS) to the risk of cancer, heart disease and other causes of death in adults who have never smoked. Draft 3 of Annex A.

Lee, P.N. (1991) Correcting meta-analyses of the association of lung cancer in females with spouse (or household) exposure for bias due to misclassification of active smoking status. Submitted to U>S. EPA, dated November 29, 1991.

Lee, P.N.; Chamberlain, J.; Alderson, M.R. (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br. J. Cancer 54:97-105.

Lee, B.L.; Benowitz, N.L.; Jacob P. (1987) Influence of tobacco abstinence of the disposition kinetics and effects of nicotine. Clin. Pharmacol. Ther. 41:474-479.

25010321101

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Leeder, S.R.; Corkhill, R.T.; Irwig, L.M.; Holland, W.W.; Colley, J.R. (1976) Influence of family factors on the incidence of lower respiratory illness during the first year of life. Br. J. Prev. Soc. Med. 30:203-212.

Lehnert, G. (1984) Roundtable discussion from symposium on medical perspectives on passive smoking. Prev. Med. 13:732-733.

Levin (1953) (p. 6-13).

Lewak, N.; van den Berg, B.J.; Beckwith, J.B. (1979) Sudden infant death syndrome risk factors. Clin. Pediatr. (Phila) 18:404-411.

Lewis, H.M.; Haeney, M.; Jeacock, J.; Thomas, H. (1989) Chronic cough in a hospital population: its relationship to atopy and defect in host defence. Arch. Dis. Child. 64:1593-1598.

Lewtas, J.; Claxton, L.; Mumford, J.L. (1987) Human exposure to mutagens from indoor combustion sources. In: Seifert, B.; Esdorn, M.; Fischer, M.; Ruden, H.; Wegner, J., eds. Indoor air '87, Vol. 1, Oraniendruck GmbH, Berlin, pp. 473-477.

Ling, P.I.; Lofroth, G.; Lewtas, J. (1987) Mutagenic determination of passive smoking. Toxicol. Lett. 35:147-151.

Liu, Z.; He, X.; Chapman, R.S. (1991) Smoking and other risk factors for lung cancer in Xuanwei, China. Int. J. Epidemiol. 20:26-31.

Löfroth, G.; Nilsson, L.; Alfeim, I. (1983) Passive smoking and urban air pollution: Salmonella/microsome mutagenicity assay of simultaneously collected indoor and outdoor particulate matter. In: Waters, M.D.; Sandhu, S.S.; Lewtas, J.; Claxton, L.; Chernoff, N.; Nesnow, S., eds. Short-term bioassays in the analysis of complex environmental mixtures, Vol. III. New York: Plenum, pp. 515-525.

Löfroth, G.; Ling, P.I.; Agurell, E. (1988) Public exposure to environmental tobacco smoke. Mutat. Res. 202:103-110.

250103210 2 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Löfroth, G.; Burtin, R.; Forehand, L.; Hammond, K.; Selia, R.; Zwiedinger, E.; Lewtas, J. (1989) Characterization of genotoxic components of environmental tobacco smoke. Environ. Sci. Technol. 23:610-614.

Lossing, E.H.; Best, E.W.R.; McGregor, J.T.; Josie, G.H.; Walker, C.B.; Delaquis, F.M.; Baker, P.M.; McKenzie, A.C. (1966) A Canadian study of smoking and health. Ottawa, Canada: Department of National Health and Welfare.

Lubin, J.H.; Blot, W.J.; Berrino, F.; Flamant, R.; Gillis, C.R.; Kunze, M.; Schmahl, D.; Visco, G. (1984) Modifying risk of developing lung cancer by changing habits of cigarette smoking. Br. Med. J. 288:1953-1956.

MacDonald, E.J. (1981) [Letter] Br. Med. J. 283:915-916.

Machlin, S.R.; Kleinman, J.C.; Madans, J.H. (1989) Validity of mortality analysis based on retrospective smoking information. Stat. Med. 8:997-1009.

Maclure, M.; Katz, R.B.-A.; Bryant, M.S.; Skipper, P.L.; Tannenbaum, S.R. (1989) Elevated blood levels of carcinogens in passive smokers. Am. J. Public Health 79:1381-1384.

Magnusson, C.G.M. (1986) Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. J. Allergy Clin. Immunol. 78:898-904.

Makin, J.; Fried, P.A.; Watkinson, B. (1991) A comparison of active and passive smoking during pregnancy: long-term effects. Neurotoxicol. Teratol. 13:5-12.

Malloy, M.H.; Kleinman, J.C.; Land, G.H.; Schramm, W.F. (1988) The association of maternal smoking with age and cause of infant death. Am. J. Epidemiol. 128:46-55.

Mantel, N. (1963) Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. J. Am. Stat. Assoc. 58:690-700.

Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

25010321O3

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Maran, A.G.D.; Wilson, J.A. (1986) Glue ear and speech development. Br. Med. J. 293:713-714.

Marbury, M.C.; Hammond, S.K.; Haley, N.J. (1990) Assessing exposure to environmental tobacco smoke in epidemiological studies of acute health effects. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2. Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 189-194.

Marchand, L.L.; Wilkens, L.R.; Hankin, J.H.; Haley, N.J. (1991) Dietary patterns of female nonsmokers with and without exposure to environmental tobacco smoke. Cancer Causes and Control 2:11-16.

Martin, T.R.; Bracken, M.B. (1986) Association of low birth weight with passive smoke exposure in pregnancy. Am. J. Epidemiol. 124:633-642.

Martinez, F.D.; Morgan, W.J.; Wright, A.L.; Holberg, C.J.; Taussig, L.M. (1988a) Diminished lung function as a predisposing factor for wheezing lower respiratory tract illness in infants. N. Engl. J. Med. 319:1112-1117.

Martinez, F.D.; Antognoni, G.; Macri, F.; Bonci, E.; Midulla, F.; De Castro, G.; Ronchetti, R. (1988b) Parental smoking enhances bronchial responsiveness in nine-year-old children. Am. Rev. Respir. Dis. 138:518-523.

Martinez, F.D.; Morgan, W.J.; Wright, A.L.; Holberg, C.; Taussig L.M. (1991a) Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Am. Rev. Respir. Dis. 143:312-316.

Martinez, F.D.; Cline, M.; Burrows, B. (1991b) Increased incidence of asthma in children of smoking mothers. Pediatrics: in press.

Masi, M.A.; Hanley, J.A.; Ernst, P.; Becklake, M.R. (1988) Environmental exposure to tobacco smoke and lung function in young adults. Am. Rev. Respir. Dis. 138:296-299.

2501032104

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Mattson, M.E.; Boyd, G.; Byar, D.; Brown, C.; Callahan, J.F.; Cullen, J.W.; Grenblatt, J.; Haley; Hammond, N.; J.F.; Lewtas, J.; Reeves, W. (1989) Passive smoking on commercial airline flights. JAMA 261:867-872.

McConnochie, K.M.; Roghmann, K.J. (1986a) Parental smoking, presence of older sibling, and family history of asthma increase risk of bronchiolitis. Am. J. Dis. Child. 140:806-812.

McConnochie, K.M.; Roghmann, K.J. (1986b) Breast feeding and maternal smoking as predictors of wheezing in children age 6 to 10 years. Pediatr. Pulmonol. 2:260-268.

Mertsola, J.; Ruuskanen, O.; Vanto, T.; Koivikko, A.; Halonen, P. (1991) Recurrent wheezy bronchitis and viral respiratory infections. Arch. Dis. Child. 66:124-129.

Meyers, D.A.; Beaty, T.H.; Freidhoff, L.R.; Marsh, D.G. (1987) Inheritance of total serum IgE (basal level) in man. Am. J. Hum. Genet. 41:51-62.

Miesner, E.A.; Rudnick, S.N.; Hu, F.; Spengler, J.D.; Preller, L.; Ozkaynak, H.; Nelson, W. (1989) Particule and nicotine sampling in public facilities and offices. J. Air Pollut. Control Assoc. 39:1577-1582.

Miller, G.H. (1984) Cancer, passive smoking and nonemployed and employed wives. West. J. Med. 140(4):632-635.

Mitchell, E.A.; Scragg, R.; Stewart, A.W.; et al. (1991) Results from the first year of the New Zealand cot death study. N.Z. Med. J. 104:71-6.

Moolgavkar, S.H.; Dewanji, A.; Luebeck, G. (1989) Cigarette smoking and lung cancer: reanalysis of the British doctors' data. J. Am. Cancer Inst. 81(6):415-420.

Moschandreas, D.J. (1981) Exposure to pollutants and daily time budgets of people. Bull. N.Y. Acad. Med. 57:845-859.

Mumford, J.L.; Lewtas, J.; Burton, R.M.; Henderson, F.W.; Forehand, L.; Allison, J.C.; Hammond, S.K. (1989) Assessing environmental tobacco smoke exposure of preschool

25010321O5

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

children in homes by monitoring air particles, mutagenicity, and nicotine. In: Measurement of toxic and related air pollutants, Environmental Protection Agency/Air and Waste Management Association international symposium. Pittsburgh, PA: Air and Waste Management Association, pp. 606-610.

Muramatsu, M.; Umemura, S.; Okada, T.; Tomita, H. (1984) Estimation of personal exposure to tobacco smoke with a newly developed nicotine personal monitor. Environ. Res. 35:218-227.

Murray, A.B.; Morrison, B.J. (1986) The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. J. Allergy Clin. Immunol. 77:575-581.

Murray, A.B.; Morrison, B.J. (1988) Passive smoking and the seasonal difference of severity of asthma in children. Chest 94:701-708.

Murray, A.B.; Morrison, B.J. (1989) Passive smoking by asthmatics: its greater effect on boys than on girls and on older than on younger children. Pediatrics 84:451-459.

Naeye, R.L.; Ladis, B.; Drage, J.S. (1976) Sudden infant death syndrome. A prospective study. Am. J. Dis. Child. 130:1207-1210.

Nagda, N.; Fortmann, R.; Koontz, M.; Konheim, A. (1990) Investigation of cabin air-quality aboard commercial airlines. In: indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 245-250.

National Institute for Occupational Safety and Health. (1991) Environmental tobacco smoke in the workplace: lung cancer and other health effects. Current Intelligence Bulletin 54. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

25010321106

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

National Research Council. (1986) Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: National Academy Press.

National Research Council. (1987) Indoor pollutants. Washington, DC: National Academy Press, p. 537.

Neal, A.D.; Wadden, R.A.; Rosenberg, S. (1978) Evaluation of indoor particulate concentrations for an urban hospital. Am. Ind. Hyg. Assoc. J. 29:578-582.

Neddenriep, D.; Martinez, F.D.; Morgan, W.J. (1990) Increased specific lung compliance in newborns whose mothers smoked during pregnancy. Am. Rev. Respir. Dis. 141:A282.

Nelson, P.A.; Qvant, F.R.; Sem, G.F. (1982) Experimental measurements of aerosol concentrations in offices. Environ. Int. 8:223-227.

Neuspiel, D.R.; Rush, D.; Butler, N.; Golding, J.; Bijur, P.E.; Kurzon, M. (1989) Parental smoking and post-infancy wheezing in children: a prospective cohort study. Am. J. Public Health 79:168-171.

NIOSH. *See* National Institute for Occupational Safety and Health.

Nitschke, I.A.; Clarke, W.A.; Clarkin, M.E.; Traynmor, G.W.; Wadach, J.B. (1985) Indoor air quality infiltration and ventilation in residential buildings. NYSERDA #85-10. Albany, NY: New York State Energy Research and Development Authority.

NRC. *See* National Research Council.

O'Connell, E.J.; Logan, G.B. (1974) Parental smoking in childhood asthma. Annals of Allergy 32:142-145.

O'Connor, G.T.; Weiss, S.T.; Tager, I.B.; Speizer, F.E. (1987) The effect of passive smoking on pulmonary function and non-specific bronchial responsiveness in a population based sample of children and young adults. Am. Rev. Respir. Dis. 135:800-804.

25010321107

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

O'Connor, G.T.; Sparrow, D.; Weiss, S.T. (1989) The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 140:225-252.

Ogden, M.W.; Nystrom, C.W.; Oldaker, G.B., III; Conrad, F.W., Jr. (1989) Evaluation of a personal passive sampling device for determining exposure to nicotine in environmental tobacco smoke. In: Measurement of toxic and related air pollutants. Pittsburgh, PA: Air Pollution Control Association, pp. 552-558.

Ogston, S.A.; Florey, C. du V.; Walker, C.M. (1987) Association of infant alimentary and respiratory illness with parental smoking and other environmental factors. J. Epidemiol. Community Health 41:21-25.

Oldaker, G.B., III; Conrad, F.W., Jr. (1987) Estimation of the effect of environmental tobacco smoke (ETS) on air quality within aircraft cabins of commercial aircraft. Environ. Sci. Technol. 21:994-999.

Oldaker, G.B.; Ogden, M.W.; Maiolo, K.C.; Conner, J.M.; Conrad, F.W.; DeLuca, P.O. (1990) Results from surveys of environmental tobacco smoke in restaurants in Winston-Salem, North Carolina. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air, Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 281-285.

Oldigs, M.; Jrres, R.; Magnussen, H. (1991) Acute effects of passive smoking on lung function and airway responsiveness in asthmatic children. Pediatr. Pulmonol. 10:123-131.

Ong, T.M.; Stewart, J.; Whong, W.Z. (1984) A simple in situ mutagenicity test for detection of mutagenic air pollutants. Mutat. Res. 139:177-181.

Park, J.K.; Kim, I.S. (1986) Effect of family smoking on acute respiratory disease in children. Yonsei Med. J. 27:261-270.

Parker, G.B.; Wilfert, G.L.; Dennis, G.W. (1984) Indoor air quality and infiltration in multifamily naval housing. Annual PNWIS/APCA meeting, Portland, OR, Nov. 12-14, pp. 1-14.

2501032108

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Pattishall, E.N.; Strope, G.L.; Etzel, R.A.; Helms, R.W.; Haley, N.J.; Denny, F.W. (1985) Serum cotinine as a measure of tobacco smoke exposure in children. Am. J. Dis. Child. 139:1101-1104.

Pedreira, F.A.; Guandolo, V.L.; Feroli, E.J.; Mella, G.W.; Weiss, I.P. (1985) Involuntary smoking and incidence of respiratory illness during the first year of life. Pediatrics 75:594-597.

Perera, F.R.; Santella, R.M.; Brenner, D.; Poirier, M.C.; Munshi, A.A.; Fischman, H.K.; Van Ryzin, J. (1987) DNA adducts, protein adducts, and sister chromatid exchange in cigarette smokers and nonsmokers. J. Natl. Cancer Inst. 79:449-456.

Pershagen, G.; Hrubec, Z.; Svensson, C. (1987) Passive smoking and lung cancer in Swedish women. Am. J. Epidemiol. 125(1):17-24.

Peto, R.; Doll, R. (1984) Keynote address: the control of lung cancer. In: Mizell, M.; Correa, P., eds. Lung cancer: causes and prevention. New York: Verlag Chemie International, pp. 1-19.

Phillips, R.L.; Garfinkel, L.; Kuzma, J.W.; et al. (1980a) Mortality among California Seventh-Day Adventists for selected cancer sites. J. Natl. Cancer Inst. 65:1097-1107.

Phillips, R.L.; Kuzma, J.W.; Beeson, W.L.; et al. (1980b) Influence of selection versus lifestyle on risk of fatal cancer and cardiovascular disease among Seventh-Day Adventists. Am. J. Epidemiol. 112:296-314.

Pierce, J.P.; Dwyer, T.; et al. (1987) Cotinine validation of self-reported smoking in commercially run community surveys. J. Chronic. Dis. 40:689-695.

Pierce, J.P.; Fiore, M.C.; Novotny, T.E.; Hatziandreu, E.J.; Davis, R.M. (1989) Trends in cigarette smoking in the United States. Projections to the year 2000. JAMA 261:61-65.

Pimm, P.E.; Silverman, F.; Shepard, R.J. (1978) Physiological effects of acute passive exposure to cigarette smoke. Arch. Environ. Health 33:201-213.

2501032109

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Pojer (1984).

Pukander, J.; Luotonen, J.; Timonen, J.; Karma, P. (1985) Risk factors affecting the occurrence of acute otitis media among 2-3-year old urban children. Acta Otolaryngol. 100:260-265.

Pullan, C.R.; Hey, E.N. (1982) Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory sycytial virus in infancy. Br. Med. J. 284:1665-1669.

Putnam, D.L.; David, R.M.; Melhorn, J.M.; Dansie, D.R.; Stone, C.J.; Henry, C.J. (1985) Dose-responsive increase in sister-chromatid exchanges in bone-marrow cells of mice exposed nose-only to whole cigarette smoke. Mutat. Res. 156:181-186.

Quant, F.R.; Nelson, P.A.; Sem, G.J. (1982) Experimental measurements of aerosol concentrations in offices. Environ. Int. 8(1-6):249-258.

Rantakallio, P. (1978) Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. Acta Paediatr. Scand. 67:621-631.

Reed, B.D.; Lutz, L.J. (1988) Household smoking exposure—association with middle ear effusions. Fam. Med. 20:426-430.

Remmer, H. (1987) Passively inhaled tobacco smoke: a challenge to toxicology and preventive medicine. Arch. Toxicol. 61:89-104.

Repace, J.L. (1987) Indoor concentrations of environmental tobacco smoke: models dealing with effects of ventilation and room size. In: O'Neill, I.K.; Brunnemann, K.D.; Dodet, B.; Hoffmann, D., eds. Environmental carcinogens—selected methods of analysis, v. 9, passive smoking. Chapter 3, IARC Monographs No. 81. Lyon, France: International Agency for Research on Cancer.

Repace, J.L. (1989) Workplace restrictions on passive smoking: justification on the basis of cancer risk (in press).

2501032110

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Repace, J.L.; Lowrey, A.H. (1980) Indoor air pollution, tobacco smoke and public health. Science 208:464-472.

Repace, J.L.; Lowrey, A.H. (1982) Tobacco smoke, ventilation and indoor air quality. Am. Soc. Heat Refrig. Air Cond. Eng. Trans. 88:894-914.

Repace, J.L.; Lowrey, A.H. (1985) A quantitative estimate of nonsmokers' lung cancer risk from passive smoking. Environ. Intl. 11:3-22.

Repace, J.L.; Lowrey, A.H. (1990) Risk assessment methodologies in passive smoking. Risk Anal. 10(1):27-37.

Riboli, E.; Preston-Martin, S.; Saracci, R.; Haley, N.J.; et al. (1990) Exposure of nonsmoking women to environmental tobacco smoke: a 10-country collaborative study. Cancer Causes and Control 1:243-252.

Rickert, W.S.; Robinson, J.C.; Collinshaw, N.E. (1984) Yields of tar, nicotine and carbon monoxide in the sidestream smoke from 15 brands of Canadian cigarettes. Am. J. Public Health 74:228-231.

Rijcken, B.; Schouten, J.P.; Weiss, S.T.; Speizer, F.E.; Van der Lende, R. (1987) The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random population sample. Am. Rev. Respir. Dis. 136:62-68.

Rimington, J. (1981) The effect of filters on the incidence of lung cancer in cigarette smokers. Environ. Res. 24:162-166.

Robins, J.M.; Blebins, D.; Schneiderman, M (1989) The effective number of cigarettes inhaled daily by passive smokers: are epidemiologic and dosimetric estimates consistent? J. Haz. Mat. 21:215-238.

Rogot, E.; Murray, J.L. (1980) Smoking and causes of death among U.S. veterans: 16 years of observation. Public Health Rep. 95:213-222.

2501032111

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Ronchetti, R.; Macri, F.; Ciofetta, G.; et al. (1990) Increased serum immunoglobulin E and increased prevalence of eosinophilia in 9-year-old children of smoking parents. J. Allergy Clin. Immunol. 86:400-407.

Rothman, K.J. (1986) Modern epidemiology. Boston: Little, Brown and Co.

Russell, M.A.H.; Feyerabend, C. (1975) Blood and urinary nicotine in nonsmokers. Lancet 1:179-181.

Russell, M.A.H.; Jarvis, M.J.; West, R.J. (1986) Use of urinary nicotine concentrations to estimate exposure and mortality from passive smoking in non-smokers. Br. J. Addict. 81:275-281.

Rylander, E.; Eriksson, M.; Freyschuss, U. (1988) Risk factors for occasional and recurrent wheezing after RSV infection in infancy. Acta Pediatr. Scand. 77:711-715.

Said, G.; Zalokar, J.; Lellouch, J.; Patois, E. (1978) Parental smoking related to adenoidectomy and tonsillectomy in children. J. Epidemiol. Community Health 32:97-101.

Samet, J.M.; Tager, I.B.; Speizer, F.E. (1983) The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. Am. Rev. Respir. Dis. 127:508-523.

Sandler, D.P.; Everson, R.B.; Wilcox, A.J. (1985) Passive smoking in adulthood and cancer risk. Am. J. Epidemiol. 121(1):37-48.

Saracci, R. (1989) Passive smoking and cancer risk. IARC report of panel of experts. Prepared at the request of the European School of Oncology through the Europe Against Cancer program of the European Economic Community.

Saracci, R.; Riboli, E. (1989) Passive smoking and lung cancer: current evidence and ongoing studies at the International Agency for Research on Cancer. Mutat. Res. 222:117-127.

Schelesselman, J.J. (1978) Assessing effects of confounding variables. Am. J. Epidemiol. 108:3-8.

2501032112

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Schelesselman, J.J. (1982) Case-control studies: design, conduct, analysis. New York: Oxford University Press.

Schenker, M.B.; Samet, J.M.; Speizer, E.F. (1983) Risk factors for childhood respiratory disease. The effect of host factors and home environment exposures. Am. Rev. Respir. Dis. 128:1038-1043.

Schenker, M.B.; Samuels, S.J.; Kado, N.Y.; Hammond, S.K.; Smith, T.J.; Woskie, S.R. (1990) Markers of exposure to diesel exhaust. Research Publication Number 33. Cambridge, MA: Health Effects Institute.

Schilling, R.S.F.; Letai, A.D.; Hui, S.L.; Beck, G.J.; Schoenberg, J.B.; Bouhuys, A. (1977) Lung function, respiratory disease, and smoking in families. Am. J. Epidemiol. 106:274-283.

Schwartz, J.; Zeger, S. (1990) Passive smoking, air pollution, and acute respiratory symptoms in a diary of student nurses. Am. Rev. Respir. Dis. 141:62-67.

Seely, J.E.; Zuskin, E.; Bouhuys, A. (1971) Cigarette smoking: objective evidence for lung damage in teen-agers. Science 172:741-743.

Seigel, D.G.; Greenhouse, S.W. (1973) Validity in estimating relative risk in case-control studies. J. Chronic Dis. 26:219-226.

Sexton, K.; Spengler, J.D.; Treitman, R.D. (1984) Personal exposure to respirable particulates: a case-study in Waterbury, Vermont. Atmos. Environ. 18:1385-1398.

Shephard, R.J. (1992) Respiratory irritation from ETS. Arch. Env. Health 47:(2):123-130.

Shephard, R.J.; Collis, R.; Silverman, F. (1979) "Passive" exposure of asthmatic subjects to cigarette smoke. Environ. Res. 20:392-402.

Sherman, C.B.; Tosteson, T.D.; Tager, I.B.; Speizer, F.E.; Weiss, S.T. (1990) Early childhood predictors of asthma. Am. J. Epidemiol. 132:83-95.

2501032113

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Sherrill, D.; Holberg, C.J.; Lebowitz, M.D. (1990) Differential rates of lung growth as measured longitudinally by pulmonary function in children and adolescents. Pediatr. Pulmonol. 8:145-154.

Shimizu, H.; Morishita, M.; Mizuno, K.; Masuda, T.; Ogura, Y.; Santo, M.; Nishimura, M.; Kunishima, K.; Karasawa, K.; Nishiwaki, K.; Yamamoto, M.; Hisamichi, S.; Tominaga, S. (1988) A case-control study of lung cancer in nonsmoking women. Tohoku J. Exp. Med. 154:389-397.

Shultz, T.M., Novotny, T.E.; Rice, D.P. (1991) Quantifying the disease impact of cigarette smoking with SAMMEC II Software. Public Health Reports 106(3)326-333.

Sidney, S.; Caan, B.; Friedman, G. (1989) Dietary intake of carotene in nonsmokers with and without passive smoke at home. Am J Epidimiol 129:1305-9.

Sims, D.G.; Downham, M.A.P.S.; Gardner, P.S.; Webb, J.K.G.; Weightman, D. (1978) Study of 8-year-old children with a history of respiratory syncytial virus bronchiolitis in infancy. Br. Med. J. 1:11-14.

Sobue, T.; Suzuki, R.; Nakayama, N.; Inubuse, C.; Matsuda, M.; Doi, O.; Mori, T.; Furuse, K.; Fukuoka, M.; Yasumitsu, T.; Kuwabara, O.; Ichigaya, M.; Kurata, M.; Nakahara, K.; Endo, S.; Hattori, S. (1990) Passive smoking among nonsmoking women and the relationship between indoor air pollution and lung cancer incidence—results of a multicenter case controlled study. Gan to Rinsho 36(3):329-333.

Somerville, S.M.; Rona, R.J.; Chinn, S. (1988) Passive smoking and respiratory conditions in primary school children. J. Epidemiol. Community Health 42:105-110.

Sparrow, D.; O'Connor, G.; Colton, T.; Barry, C.L.; Weiss, S.T. (1987) The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary function. The normative aging study. Am. Rev. Respir. Dis. 135:1255-1260.

2501032114

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Speizer, F.E.; Ferris, B., Jr.; Bishop, Y.M.; Spengler, J. (1980) Respiratory disease rates and pulmonary function in children associated with NO exposure. Am. Rev. Respir. Dis. 121:3-10.

Spengler, J.D.; Dockery, D.W.; Turner, W.A.; Wolfson, J.M.; Ferris, B.G. (1981) Long-term measurements of respirable sulphates and particles inside and outside homes. Atmos. Environ. 15:23-30.

Spengler, J.D.; Treitman, R.D.; Tosteson, T.D.; Mage, D.T.; Soczek, M.L. (1985) Personal exposures to respirable particulates and implications for air pollution epidemiology. Environ. Sci. Technol. 19:700-707.

Spitzer, W.O.; Lawrence, V.; Dales, R.; Hill, G.; Archer, M.C.; Clark, P.; Abenhaim, L.; Hardy, J.; Sampalis, J.; Pinfold, S.P.; Morgan, P.P. (1990) Links between passive smoking and disease: a best evidence synthesis. A report of the working group on passive smoking. Clin. Invest. Med. 13:17-42.

Stahlman, M.T.; Gray, M.E. (1984) Ontogeny of neuroendocrine cells in human fetal lung. I. An electron microscopic study. Lab. Invest. 51:449-463.

Stanton, M.F.; Miller, E.; Wrench, C.; Blackwell, R. (1972) Experimental induction of epidermoid carcinoma in the lungs of rats by cigarette smoke condensate. J. Natl. Cancer Inst. 49:867-877.

Steele, R.; Langworth, J.T. (1966) The relationship of antenatal and postnatal factors to sudden unexpected death in infancy. Can. Med. Assoc. J. 94:1165-1171.

Steenland, K. (1992) Passive smoking and the risk of heart disease. JAMA 267:94-99.

Stellman, S. D.; Garfinkel, L. (1986) Smoking habits and tar levels in a new American Cancer Society prospective study of 1.2 million men and women. J. Natl. Cancer Inst. 76(6):1057-1063.

2501032115

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Sterling, T.D.; Sterling, E.M. (1983) Investigations on the effect of regulating smoking on levels of indoor pollution and on the preception of health on comfort of office workers. Eur. J. Respir. Dis. 65 (Suppl. 133):17-32.

Stockwell (1990) (p. B-7).

Stockwell, H.G.; Candelora, E.C.; Armstrong, A.W.; Pinkham, P.A. (1991) Environmental tobacco smoke and lung cancer in never smoking women. Presented at the annual meeting abstract forum: Society for Epidemiologic Research, June 12-14, 1991, Buffalo, New York.

Strachan, D.P. (1988) Damp housing and childhood asthma: validation of reporting of symptoms. Br. Med. J. 297:1223-6.

Strachan, D.P.; Jarvis, M.J.; Feyerabend, C. (1990) The relationship of salivary cotinine to respiratory symptoms, spirometry, and exercise-induced bronchospasm in seven-year-old children. Am. Rev. Respir. Dis. 142:147-151.

Strachan, D.P.; Jarvis, M.J.; Feyerabend, C. (1989) Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. Br. Med. J. 298:1549-1552.

Sutton (1980) (p. B-14).

Svendsen, K.H.; Kuller, L.H.; Martin, M.J.; Ockene, J.K. (1987) Effects of passive smoking in the multiple risk intervention trial. Am. J. Epidemiol. 126:783-795.

Svensson, D. (1988) Lung cancer etiology in women. [Dissertation] Karolinska Institute, Stockholm, Sweden.

Svensson, C.; Pershagen, G.; Klominek, J. (1988) Smoking and passive smoking in relation to lung cancer in women. Department of Epidemiology, National Institute of Environmental Medicine, Stockholm, Sweden.

Svensson, C.; Pershagen, G.; Klominek, J. (1989) Smoking and passive smoking in relation to lung cancer in women. Acta Oncol. 28:623-629.

2501032116

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Tager, I.B.; Segal, M.R.; Munoz, A.; Weiss, S.T.; Speizer, F.E. (1987) The effect of maternal smoking on the pulmonary function of children and adolescents. Analysis of data from two populations. Am. Rev. Respir. Dis. 136:1366-1370.

Tager, I.B.; Weiss, S.T.; Munoz, A.; Rosner, B.; Speizer, F.E. (1983) Longitudinal study of the effects of maternal smoking on pulmonary function in children. N. Engl. J. Med. 309:699-703.

Tager, I.B.; Weiss, S.T.; Rosner, B.; Speizer, F.E. (1979) Effect of parental cigarette smoking on the pulmonary function of children. Am. J. Epidemiol. 110:15-26.

Tainio, V.M.; Savilahti, E.; Salmenpera, L.; Arjomaa, P.; Siimes, M.A.; Perheentupa, J. (1988) Risk factors for infantile recurrent otitis media: atopy but not type of feeding. Pediatr. Res. 23:509-12.

Takasaka, T. (1990) Incidence, prevalence, and natural history of otitis media in different geographic areas and populations. Ann. Otol. Rhinol. Laryngol. 99:13-14.

Tashkin, D.P.; Clark, V.A.; Simmons, M.; Reems, C.; Coulson, A.H.; Bourque, L.B.; Sayre, J.W.; Detels, R.; Rokaw, S. (1984) The UCLA population studies of chronic obstructive respiratory disease. VII. Relationship between parental smoking and children's lung function. Am. Rev. Respir. Dis. 129:891-897.

Taylor, R.G.; Gross, E.; Joyce, H.; Holland, F.; Pride, N.B. (1985) Smoking, allergy, and the differential white blood cell count. Thorax 40:17-22.

Teele, D.W.; Klein, J.O.; Rosner, B. (1989) Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. J. Infect. Dis. 160: 83-94.

Toyoshima, K.; Hayashida, M.; Yasunami, J.; Takamatsu, I.; Niwa, H.; Muraoka, T. (1987) Factors influencing the prognosis of wheezy infants. J. Asthma. 24:267-270.

2501032117

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Trichopoulos, D.; Kalandidi, A.; Sparros, L. (1983) Lung cancer and passive smoking: conclusion of Greek study. [Letter] Lancet 667-668.

Trichopoulos, D.; Kalandidi, A.; Sparros, L.; MacMahon, B. (1981) Lung cancer and passive smoking. Int. J. Cancer 27:1-4.

Trichopoulos, D. (1988) Passive smoking and lung cancer. Scand. J. Soc. Med. 16:75-79.

Tsimoyianis, G.V.; Jacobson, M.S.; Feldman, J.G.; Antonio-Santiago, M.T.; Clutario, B.C.; Nussbaum, M.; Shenker, I.R. (1987) Reduction in pulmonary function and increased frequency of cough associated with passive smoking in teenage athletes. Pediatrics 80:32-36.

Uberla, K.; Ahlborn, W. (1987) Passive smoking and lung cancer; a reanalysis of Hirayama's data. In: Proceedings of international conference on indoor air quality. Tokyo: Council for Environment and Health, p. 41.

U.S. Bureau of the Census (1990). Statistical abstract of the United States, 1990.

U.S. Department of Health and Human Services. (1982) The health consequences of smoking: cancer. A report of the Surgeon General. U.S. Department of Health and Human Services, Public Health Service.

U.S. Department of Health and Human Services. (1983) The health consequences of smoking: cardiovascular disease. A report of the Surgeon General. DHHS Pub. No. (PHS) 84-50204. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.

U.S. Department of Health and Human Services. (1984) The health consequences of smoking: chronic obstructive lung disease. A report of the Surgeon General. DHHS Pub. No. (PHS) 84-50205. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.

2501032118

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

U.S. Department of Health and Human Services. (1986) The health consequences of involuntary smoking. A report of the Surgeon General. DHHS Pub. No. (PHS) 87-8398. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.

U.S. Department of Health and Human Services. (1989) Reducing the health consequences of smoking: 25 years of progress. A report of the Surgeon General. U.S. Department of Health and Human Services, Public Health Service.

U.S. Department of Health and Human Services. (1990) The health benefits of smoking cessation. A report of the Surgeon General. U.S. Department of Health and Human Services, Public Health Service.

U.S. Department of Health and Human Services. (1990b) Vital and health statistics: current estimates from the national health interview survey, 1989. p.129.

U.S. Department of Health, Education, and Welfare. (1964) Smoking and health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. PHS Pub. No. 1103.

U.S. Department of Health, Education, and Welfare. (1977) Nicotine. NIOSH manual of analytical methods, Vol. 3, 2nd Ed., Publication No. 77-157-C.

U.S. DHEW. *See* U.S. Department of Health, Education, and Welfare.

U.S. DHHS. *See* U.S. Department of Health and Human Services.

U.S. Department of Transportation. (1971) Health aspects of smoking in transport aircraft. Washington, DC: U.S. Department of Transportation, National Technical Information Service.

U.S. Environmental Protection Agency. (1986a) Guidelines for carcinogen risk assessment. Federal Register 51:33992-34003.

2501032119

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

U.S. Environmental Protection Agency. (1986b) Guidelines for the health risk assessment of chemical mixtures. Federal Register 51:34014-34025.

U.S. Environmental Protection Agency. (1989) Workshop report on EPA guidelines for carcinogen risk assessment: Use of human evidence, September 1989.

U.S. Environmental Protection Agency (EPA). (1990) Health effects of passive smoking: assessment of lung cancer in adults and respiratory disorders in children. External Review Draft. EPA/600/6-90/006A.

U.S. EPA. *See* U.S. Environmental Protection Agency.

Varela, L.R. (1987) Assessment of the association between passive smoking and lung cancer. [doctoral dissertation]. New Haven, CT: Yale University.

Vaughan, W.M.; Hammond, S.K. (1990) Impact of designated smoking area. Policy on nicotine vapor and particle concentrations in a modern office building. J. Air Waste Management Assoc. 40:1012-1017.

Vedal, R.E.; Schenker, M.B.; Samet, J.M.; Speizer, F.E. (1984) Risk factors for childhood respiratory disease. Am. Rev. Respir. Dis. 130:187-192.

Vidic, B.; Ujevic, N.; Shabahang, M.M.; Van de Zande, F. (1989) Differentiation of interstitial cells and stromal proteins in the secondary septum of early postnatal rat: effect of maternal chronic exposure to whole cigarette smoke. Anat. Rec. 165:165-173.

Vincent, T.N.; Satterfield, J.V.; Ackerman, L.V. (1965) Carcinoma of the lung in women. Cancer 18:559-570.

Vincent, R.G.; Pickren, J.W.; Lane, W.W.; Bross, I.; Takita, H.; Houten, L.; Gutierrez, A.C.; Rzepka, T. (1977) The changing histopathology of lung cancer: a review of 1682 cases. Cancer 39:1647-1655.

Vutuc, C. (1984) Quantitative aspects of passive smoking and lung cancer. Prev. Med. 13:698-704.

2501032120

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Wald, N.J.; Boreham, J.; Bailey, A.; et al. (1984) Urinary cotinine as a marker of breathing other people's tobacco smoke. Lancet 1:230-231.

Wald, N.J.; Ritchie, C. (1984) Validation of studies on lung cancer in nonsmokers married to smokers. Lancet 1:1067.

Wald, N.J.; Nanchahal, K.; Thompson, S.G.; Cuckle, H.S. (1986) Does breathing other people's tobacco smoke cause lung cancer? Br. J. Med. 293:1217-1222.

Wall, M.; Johnson, J.; Jacob, P.; Benowitz, N. (1988) Cotinine in the serum, salivia, and urine of nonsmokers, passive smokers, and active smokers. Am. J. Public Health 78:699-701.

Wang, N.S.; Chen, M.F.; Schraufnagel, D.E. (1984) The cumulative scanning electron microscopic changes in baby mouse lungs following prenatal and postnatal exposures to nicotine. J Pathol. 144:89-100.

Ware, J.H.; Dockery, D.W.; Spiro, A., III.; Speizer, F.E.; Ferris, B.G., Jr. (1984) Passive smoking, gas cooking, and respiratory health of children living in six cities. Am. Rev. Respir. Dis. 129:366-374.

Weber A.; Fischer T.; Grandjean, A. (1979) Passive smoking in experimental and field conditions. Environ. Res. 20:205-216.

Weir, J.M.; Dunn, J.E., Jr. (1970) Smoking and mortality: a prospective study. Cancer 25:105-112.

Weiss, W.; Boucot, K.R.; Seidman, H.; Carnahan, W.J. (1972) Risk of lung cancer according to histologic type and cigarette dosage. JAMA 222:799-801.

Weiss, S.T.; Tager, I.B.; Speizer, F.E.; Rosner, B. (1980) Persistent wheeze: its relation to respiratory illness, cigarette smoking, and level of pulmonary function in a population sample of children. Am. Rev. Respir. Dis. 122:697-707.

2501032121

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Weiss, S.T.; Tager, I.B.; Munoz, A.; Speizer, F.E. (1985) The relationship of respiratory infections in early childhood to the occurrence of increased levels of bronchial responsiveness and atopy. Am. Rev. Respir. Dis. 131:573-578.

Weitzman, M.; Gortmaker, S.; Klein Walker, D.; Sobol, A. (1990) Maternal smoking and childhood asthma. Pediatrics 85:505-11.

Wells, A.J. (1988) An estimate of adult mortality in the United States from passive smoking. Environ. Int. 14:249-265.

Wells, A.J. (1990) Smoker misclassification does not account for observed passive smoking risk for lung cancer. Submission to Indoor Air Quality and Total Human Exposure Committee, Science Advisory Board, U.S. EPA, December 4, 1990.

White, J.R.; Froeb, H.F. (1980) Small airways dysfunction in nonsmokers chronically exposed to tobacco smoke. N. Engl. J. Med. 302:720-723.

Whittemore, A.S. (1988) Effect of cigarette smoking in epidemiological studies of lung cancer. Stat. Med. 7:223-238.

Wigle, D.T.; Collishaw, N.E.; Kirkbride, J.; Mao, Y. (1987) Deaths in Canada from lung cancer due to involuntary smoking. J. Can. Med. Assoc. 136:945-_____.

Willatt, D.J. (1986) Children's sore throats related to parental smoking. Clin. Otolaryngol. 11:317-321.

Williamson, D.F.; Serdula, M.K.; Kendrick, J.S.; Binkin, N.C. (1989) Comparing the prevalence of smoking in pregnant and nonpregnant women, 1985 to 1986. JAMA 261:70-74.

Woodward, A.; Douglas, R.M.; Graham, N.M.H.; Miles, H. (1990) Acute respiratory illness in Adelaide children: breast feeding modifies the effect of passive smoking. J. Epidemiol. Community Health 44:224-30.

2501032122

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Woolcock, A.J.; Peat, J.K.; Leeder, S.R.; Blackburn, C.R.B. (1984) The development of lung function in Sydney children: effects of respiratory illnesss and smoking. A ten year study. Eur. J. Resp. Dis. 65(Suppl):1-137.

Woolcock, A.J.; Peat, J.K.; Salome, C.M.; et al. (1987) Prevalence of bronchial hyperresponsivess and asthma in a rural adult population. Thorax 42:361-368.

Woolf, B. (1955) On estimating the relationship between blood group and disease. Ann Human Genet 19:251-253.

Wright, A.L.; Taussig, L.M.; Ray, C.G.; Harrison, H.R.; Holberg, C.J. (1989) The Tucson's children respiratory study. II. Lower respiratory tract illnesses in the first year of life. Am. J. Epidemiol. 129:1232-1246.

Wright, A.L.; Holberg, C.; Martinez, F.D.; Taussig, L.M. (1991) Relationship of parental smoking to wheezing and non-wheezing lower respiratory tract illnesses in infancy. J. Pediatr. 118:207-214.

Wu, A.H.; Henderson, B.E.; Pike, M.D.; Yu, M.C. (1985) Smoking and other risk factors for lung cancer in women. J. Natl. Cancer Inst. 74(4):747-751.

Wu-Williams, A.H.; Samet, J.H. (1990) Environmental tobacco smoke: exposure-response relationships in epidemiologic studies. Risk Anal. 10:1.

Wynder, E.L.; Hoffmann, D. (1967) Tobacco and tobacco smoke: studies in experimental carcinogenesis. New York: Academic Press.

Wynder, E.L.; Stellman, S.D. (1977) Comparative epidemiology of tobacco-related cancers. Cancer Res. 37:4608-4622.

Wynder, E.L.; Gottlieb, S.; Wright, G. (1957) A study of tobacco carcinogenesis. IV. Different tobacco types. Cancer 10:1206-1209.

2501032123

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Wynder, E.L.; Mabuchi, K.; Beattie, E.J., Jr. (1970) The epidemiology of lung cancer: recent trends. JAMA 213:2221-2228.

Xu, Z.Y.; Blot, W.J.; Xiao, H.P.; et al. (seven others) (1989) Smoking, air pollution and the high rates of lung cancer in Shenyand, China. J. Natl. Cancer Inst. 81:1800.

Yarnell, J.W.; St Leger, A.S. (1979) Respiratory illness, maternal smoking habit and lung function in children. Br. J. Dis. Chest 73:230-236.

Young, S.; LeSouef, P.N.; Reese, A.C.; Stick, S.M.; Landau, L.I. (1990) Factors predicting cough and wheeze in the first 6 months of life. Am. Rev. Respir. Dis. 141:A901.

Zahm, S.H.; Cocco, P.; Blair, A. (1991) Tobacco smoking as a risk factor for colon polyps. Am. J. Public Health 81:846-849.

Zetterstrom, O.; Osterman, K.; Machado, L.; Johansson, S.G.O. (1981) Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. Br. Med. J. 283:1215-1217.

2501032124

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

APPENDIX A

REVIEWS OF EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

250103212S

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

CONTENTS

A.1.	INTRODUCTION	A-1
A.2.	AKIB	A-1
A.3.	BROW	A-5
A.4.	BUFF	A-8
A.5.	BUTL(Coh)	A-10
A.6.	CHAN	A-13
A.7.	CORR	A-16
A.8.	FONT	A-19
A.9.	GAO	A-25
A.10.	GARF (Case-Control)	A-28
A.11.	GARF(Coh)	A-33
A.12.	GENG	A-38
A.13.	HIRA(Coh)	A-40
A.14.	HOLE(Coh)	A-51
A.15.	HUMB	A-53
A.16.	INOU	A-56
A.17.	JANE	A-58
A.18.	KABA	A-63
A.19.	KALA	A-66
A.20.	KATA	A-71
A.21.	KOO	A-73
A.22.	LAMT	A-78
A.23.	LAMW	A-81
A.24.	LEE	A-84
A.25.	LIU	A-89
A.26.	PERS	A-92
A.27.	SHIM	A-96
A.28.	SOBU	A-99
A.29.	STOC	A-102

250103212G

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

CONTENTS (continued)

A.30. SVEN A-103
A.31. TRIC A-106
A.32. WU A-110
A.33. WUWI A-115

2501032127

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.1. INTRODUCTION

This appendix contains a review of each epidemiologic study based on the primary references listed in Table 5-1. Descriptions of the four prospective cohort studies are individualized according to the requirements of each study—for example, HIRA(Coh) has a long history of controversy in the literature, so the main arguments are chronicled and discussed as part of the review. Reviews of case-control studies follow a structured format, consisting of three parts: (1) the author's abstract, which summarizes the most salient features and conclusions in the author's opinion; (2) a study description based on the contents of a completed study format designed around principles of good epidemiologic practice and features specific to environmental tobacco smoke (ETS); and (3) a section of comments related to evaluation and interpretation of the study. The author's abstract is, of course, entirely his words; the study description is intended to portray accurately the reference article vis-à-vis items in the study format, so the author's words are used when possible; the comments section is entirely our own assessment of characteristics relevant to study interpretation and utility in this report.

Only an abstract is available for the case-control study by Stockwell et al., referred to as STOC, which has not appeared in print yet. There is insufficient information on the study to include it in the main body of this report. Similarly, only an abstract is available for the second study of Kabat and Wynder, which is included in an addendum following the review of their first study, KABA. The data for many of the studies reviewed have been extracted from a larger, more comprehensive study that includes active smokers. The subjects and their data used for investigation of an association between ETS exposure and lung cancer incidence are referred to as "ETS subjects" and "ETS data," respectively.

A.2. AKIB

A.2.1. Author's Abstract

"A case-control study conducted in Hiroshima and Nagasaki, Japan, revealed a 50% increased risk of lung cancer among nonsmoking women whose husbands smoked. The risks tended to increase with amount smoked by the husband, being highest among women who worked outside the home and whose husbands were heavy smokers, and to decrease with cessation of exposure. The findings provide incentive for further evaluation of the relationship between passive smoking and cancer among nonsmokers."

2501032128

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.2.2. Study Description

This community-based case-control study was conducted in Hiroshima and Nagasaki, Japan, in 1982. The data collected on passive smoking are part of a larger investigation of lung cancer among atomic bomb survivors, the principal objective of which is to evaluate the interactive roles of cigarette smoking and ionizing radiation. This article reports on married female never-smokers, an unmatched subset of the data from the whole study.

The whole study includes a total of 525 primary lung cancer cases diagnosed between 1971 and 1980. Cases were identified from the Hiroshima and Nagasaki Tumor and Tissue Registries and other records. Controls were selected from among the cohort members without lung cancer, two per case in Hiroshima and three per case in Nagasaki. The controls were individually matched to the cases with respect to year of birth (± 2 years), city of residence (Hiroshima or Nagasaki), sex, biennial medical examinations, and vital status. The majority of cases were deceased; those cases were matched to decedent controls by year of death (± 3 years), in addition to the other criteria. Controls were selected from causes of death other than cancer and chronic respiratory disease. Face-to-face interviews were conducted for 81% (82%) of the eligible cases (controls), but 80% to 85% of the interviews for both cases and controls were actually conducted with the subject's next-of-kin. The mean age of cases at diagnosis is 72.1 years (range 36-94) for males and 70.2 (range 35-95) for females, which is high for lung cancer in Japan. Fifty-seven percent of the cases were pathologically confirmed; the remaining 43% were diagnosed by radiological or clinical findings.

ETS exposure in adulthood was assessed by spousal smoking status, including the average number of cigarettes smoked per day, age the spouse started smoking, and, for those who stopped smoking, the age at cessation. For childhood exposure, a single question was asked regarding whether the subject's mother or father or both smoked when the subject was living at home as a child; responses were obtained for only two-thirds of the subjects. No specific information on exposure to smoking by other household members' smoking or to smoking in the workplace was obtained. ETS exposure data were checked by comparing smoking status with records from RERF surveys in 1964-68 (self-reported by subjects when they were alive). Cases and controls who had never married were excluded. Of the female cases exposed to spousal smoking, 16% had squamous or small cell carcinoma, whereas no unexposed cases had those cell types. No information was provided on location of the carcinomas.

The number of female cases exposed to ETS is 73 out of 94 (number exposed/total) compared with 188 out of 270 female controls (crude odds ratio [OR] is 1.52 [95% C.I. = 0.88-2.63], by our calculations). Application of logistic regression to the whole study that *includes*

2501032129

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

active smokers, gives an adjusted odds ratio of 1.5 (90% C.I. = 1.0-2.5), similar to the crude analysis. It is not stated explicitly that matching variables were included in the logistic regression model. Four additional analyses were conducted on the ETS data alone (i.e., without active smokers). The authors stratified exposure by number of cigarettes smoked per day by husband (0, 1-19, 20-29, 30+) and obtained a marginally significant trend ($p = 0.06$). No dose-response gradient was found in the association between the number of years the husband smoked cigarettes and the risk of lung cancer in female never-smokers; the odds ratio *decreases* from lowest to highest exposure level (2.1, 1.5, and 1.3). Stratified analysis according to recency of exposure to husband's smoking (unexposed, exposed but not within the past 10 years, and exposed within the past 10 years) shows a significant upward trend ($p = 0.05$). Further stratification of exposed subjects by occupation found that lung cancer risk tends to increase across occupational categories in the following order: housewife, white collar worker, blue collar worker. The highest odds ratio occurred for women who had blue collar jobs and were married to men who smoked one or more packs of cigarettes per day, but the number involved was small. It is reported that additional analyses on the data indicated that factors for matching in the whole study have little influence, but the details are omitted.

Limited histological information is provided. Among cases exposed to spousal smoking, 16% had squamous or small cell cancer, and 84% had adenocarcinoma or large cell cancer. All of the unexposed cases had adenocarcinoma.

The authors conclude that there may be a moderate excess in lung cancer risk associated with passive smoking. The odds ratio for lung cancer among nonsmoking women tends to increase with amount smoked by their husbands, a trend seen among housewives, as well as among women who work outside the home. There was little association with parental smoking or from passive smoking that had ceased more than 10 years previously.

A.2.3. Comments

The larger study from which the ETS data are taken was primarily intended to investigate the interaction of smoking and ionizing radiation in atomic bomb survivors of Nagasaki and Hiroshima. The information on passive smoking has been collected posthumously in a large percentage of the cases, requiring heavy use of proxy responses. The response rate was not high, however, because of the refusal of next-of-kin to answer questions about deceased relatives and lack of attempt to locate next-of-kin to answer questions about some subjects who had died or moved away from Hiroshima or Nagasaki. The dependence on proxy respondents raises questions about the validity of the exposure data for some measures, particularly in childhood, and about

2501032130

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

detailed information such as the number of cigarettes smoked per day, duration of smoking habit, and years since cessation of smoking. Information on childhood exposure was obtained for only two-thirds of the subjects. The omission of data on subjects where the next-of-kin had refused response or the subject had moved may be a source of bias. The diagnosis of lung cancer was not pathologically confirmed in over 40% of the cases. Even if the data were complete and accurate on all subjects, however, it is not clear that the subjects are representative of the target population. They had been exposed to ionizing radiation to varying degrees, whatever implication that may have; they are among the survivors, which may suggest selective characteristics; and their age distribution is high, ranging from about 35 to 90 years of age with an average of 70 or more years.

Only ever-marrieds are included in the ETS subjects, which is helpful in the analysis. There is some ambiguity in the statistical analyses, however, in reference to Tables 2 through 6 (the main results). The tables contain odds ratios that are reported to be the result of logistic regression with matching. The details regarding matching in the analysis are not given, but it is reported that analysis of the crude data and matched logistic regression give similar values. Regarding the analyses for trend, the outcome seems to be sensitive to the measure of exposure used. The odds ratio are strictly increasing for stratification by number of cigarettes smoked per day, but a different pattern emerges when ETS exposure is measured by the number of years the husband smoked cigarettes.

In general, the conclusions are presented more strongly than the data warrant. The assertions are somewhat tenuous that risks tend to increase with amount smoked by the husband, are highest among those who worked outside the home and whose husbands are heavy smokers, and decrease with cessation of smoking. Conversely, whereas little association between ETS exposure in childhood and lung cancer is reported, relevant information was available for only two-thirds of the subjects, and its accuracy is questionable because most of that information was provided by proxies. Overall, the observed data suggest that ETS exposure may be related to risk of lung cancer, but there is some potential for misclassification and other sources of bias. Thus, this study provides some useful information on lung cancer risk in passive smokers, but its interpretation needs to be more conservative, taking into account the atypical characteristics of the subjects and other concerns described above.

2501032131

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.3. BROW

A.3.1. Author's Abstract

"The relation between various risk factors and adenocarcinoma of the lung was evaluated in a case-control study. Subjects were selected from the Colorado Central Cancer Registry from 1979-82 in the Denver metropolitan area. A total of 102 (50 males and 52 females) adenocarcinoma case interviews and 131 (65 males and 66 females) control interviews were completed. The control group consisted of persons with cancers of the colon and bone marrow. The risk estimates associated with cigarette smoking were significantly elevated among males (odds ratio [OR] = 4.49) and females (OR = 3.95) and were found to increase significantly ($p < 0.01$) with increasing levels of cigarette smoking for both males and females. For adenocarcinoma in females, the age- and smoking-adjusted odds ratios at different levels of passive smoke exposure followed an increasing overall trend ($p = 0.05$). After additional adjustment for potential confounders, prior cigarette use remained the most significant predictor of risk of adenocarcinoma among males and females. Analysis restricted to nonsmoking females revealed a risk of adenocarcinoma of 1.68 (95% confidence interval [C.I.] = 0.39-2.97) for passive smoke exposure of four or more hours per day. Neither sex showed significantly elevated risk for occupational exposures, although males bordered on significance (OR = 2.23, 95% C.I. = 0.97-5.12). The results suggest the need to develop cell type-specific etiologic hypotheses."

A.3.2. Study Description

This study was conducted in Denver, Colorado, to evaluate the role of smoking, passive smoking, occupation, community air pollution, and socioeconomic status in the etiology of adenocarcinoma of the lung. Because subjects include active smokers, the data on ETS subjects are part of a larger data set.

Cases and controls were drawn from the Colorado Central Cancer Registry. All subjects were diagnosed with lung adenocarcinoma between 1979 and 1982. Cases are white female Denver residents of at least 6 months' duration. Controls are of similar description to the cases, except that they were diagnosed with colon cancer or bone marrow cancer. Controls were matched on a group basis to produce the same age and gender composition. It is not clear if incident cases were used and whether control sampling was cumulative or density.

The subjects are not matched on smoking status, so the data on ETS subjects alone are unmatched for all variables considered in the larger study. Face-to-face interviews were conducted, blindly, on a total of 149 cases and 169 controls, after attrition in selection and follow-up of 47 cases and 38 controls. The subject was interviewed in 31% of the cases and 61% of the

2501032132

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

controls; the remaining interviews were conducted with a friend or relative. The mean age of the female cases (controls) was 64.9 (68.2) years; no further details are provided. Clinical verification of lung cancer diagnosis was conducted microscopically.

"Exposed" to ETS is used in two ways, depending on context: (1) the husband smoked (presumably "ever-smoked" is intended, rather than "currently smokes," but that is not explicit); (2) the subject was in the presence of tobacco smoke, from any source, 4 or more hours per day on average. Although there are two operational definitions of exposure, neither includes duration of ETS exposure. Questions were apparently asked regarding exposure in both childhood and adulthood, the latter including sources in the home and in the workplace. No indication was found that the data collected from subjects was checked for internal consistency or against other sources. No mention was found regarding the number of unmarried women in the study or what assumptions may have been made regarding their exposure to ETS when spousal smoking is the source considered (the first of the definitions given above).

The ETS subjects consist of 4 out of 19 (exposed/total) female cases and 7 out of 47 controls, when ETS exposure means the spouse smoked (Definition 1). For exposure from all sources (Definition 2), the corresponding numbers for cases and controls are 4 out of 19 and 6 out of 47, respectively. The crude odds ratio is 1.52 (95% C.I. = 0.39-5.96) for Definition 1 of ETS exposure and 1.82 (95% C.I. = 0.45-7.36) for Definition 2 (data communicated from first author, Brownson). A test for trend using hours per day as the exposure measure is conducted on the whole data set for females *including smokers* (33 of 52 cases are smokers and 19 of 66 controls are smokers; the two exposure categories, 4 to 7 and 8 or more hours per day of exposure to passive smoke, contain a total of only 4 cases and 6 controls who are nonsmokers, but 19 cases and 7 controls who are smokers). The method of Miettenen is applied with stratification on age and smoker status ($p = 0.05$ for trend). The data for never-smokers alone were used in a multiple logistic regression to compare subjects exposed 0 to 3 hours per day with those exposed from all sources 4 or more hours per day (Definition 2 of ETS exposure). Adjustments were made for age, income, and occupation. The reported odds ratio is 1.68 (95% C.I. = 0.39-2.97). (*Note:* It appears that the upper confidence value may be in error. In view of the outcome for the crude odds ratio, a value about twice what is shown might be anticipated.)

To summarize the statistical tests and authors' conclusions, no significant risk estimates were shown when smoking by the spouse was considered as a dichotomous variable. When the data for both active smokers and passive smokers were stratified according to level of passive smoke exposure, a statistically significant trend in the risk estimates was shown for females ($p = 0.05$) after adjustment for age and cigarette smoking. However, after adjustment by logistic

2501032133

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

regression for age, income, occupation, and cigarette smoking, with the two exposure categories for ETS combined (> 3 and 4+ hours per day), no significant risk was detected.

A.3.3. Comments

The study is very small when reduced to the never-smokers alone. The measure of ETS exposure used (hours/day from all sources) is not very specific to differentiate exposed from unexposed persons, particularly exposure 20 to 30 years ago, which may be more relevant than current exposure. Only 15% of the controls have a husband who smoked; only 13% of ETS subjects are exposed from any source 4 or more hours per day. Thus, the cut-point selected by the researchers for general ETS exposure (4+ hours/day) may be too high, resulting in a substantial amount of exposure in the "unexposed" group. For either definition of ETS exposure, however, the percentage exposed is extremely low. Details are lacking also in other areas that may have a bearing (e.g., the treatment of unmarried subjects—whether they were present and, if so, the assumption made regarding ETS exposure).

We experienced some difficulty with the statistical analyses. One of the adjusted procedures is the trend test. Perhaps because the number of ETS subjects is so small, smokers were included in the analysis and then a method was used to attempt to adjust the effects of their presence on the outcome. The only value that leaving the smokers in the analysis would serve, that we can see, would be if one believes that they contribute to the evidence on lung cancer and passive smoking. That seems doubtful. There are so few ETS subjects in the exposure categories (see above) that it seems highly unlikely that a test for trend would be significant if based on the ETS subjects alone (we did not have the number of ETS subjects by exposure group, however, so we were unable to conduct the trend test to check the outcome).

When the two exposure categories were combined and only the ETS subjects used, the results were not close to statistically significant (OR is 1.68; 95% C.I. = 0.39-2.97). We also had a problem with that result. When a statistical procedure is used to determine which variables to adjust for in using another procedure with the same data, it may distort the statistical interpretation. There also may be a typographical error in the upper confidence limit because the value shown is only about half the corresponding value for the crude odds ratio.

The remaining analyses are from the crude odds ratio, 1.52 (95% C.I. = 0.39-5.99) and 1.82 (95% C.I. = 0.45-7.36), which suggests a possible association between ETS exposure and lung cancer, although it could easily be ascribed to chance in view of the wide confidence intervals. The study has a very strict requirement for classification as exposed to ETS (4+ hours per day), which is reflected in only 15% of the controls being designated as exposed (40-60% is more

250103213 4

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

typical). The 12% figure based on simply being married to a smoker, however, is no better. The control subjects are unlikely to be a representative sample of the target population, or else the classification of subjects exposed is too rigid. The crude odds ratio may be the preferred statistical measure to represent the outcome of the data, but care should be exercised in using the results from this study in conjunction with those of other studies.

A.4. BUFF

A.4.1. Author's Abstract

"A population-based case-comparison interview study of lung cancer was conducted from 1979 to 1982 in six Texas coastal counties—Orange, Jefferson, Chambers, Harris, Galveston, and Brazoria—to evaluate the association of lung cancer with occupational and other environmental exposures. Lung cancer mortality rates in these counties consistently have exceeded lung cancer mortality rates observed for Texas and the United States from 1950-69 to 1970-75 for both sexes and races (white and nonwhites).

Histologically and cytologically confirmed incident cases diagnosed during the interval July 1976 to June 1980 among white male and female residents ages 30 to 79 years were ascertained from participating hospitals in the six-county area. Both population-based and decedent comparisons were selected and matched on age, race, sex, region of residence, and vital status at time of ascertainment. The exposures of primary interest in the study of lung cancer are those associated with occupation (employment in specific industries and occupations) in conjunction with tobacco, alcohol, diet, and residential exposures."

A.4.2. Study Description

This population-based case-control study was conducted in six coastal counties of eastern Texas to evaluate the association of lung cancer with occupational and other environmental exposures. Those of primary interest are associated with occupation in conjunction with tobacco, alcohol, diet, and residential exposures. The ETS subjects are part of this larger study that includes active smokers.

Cases include males and females ascertained from hospital and state records during 1976-80, except for Harris County, which includes only females from 1977-80. All subjects are white (including Hispanic) county residents of at least 6 months. Cases are incident, without restriction to cell type, and histologically diagnosed to eliminate secondary lung cancers (there is some inconsistency in the article on whether all diagnoses were by histology or whether some were by cytology). Controls were selected from State and Federal records, group matched on age, sex,

2501032135

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

race or ethnicity, county of residence, and vital status. The candidate sample size is estimated in the report at approximately 1,650, including both sexes, of which just over 700 were lost to attrition in selection or follow-up for various reasons. Face-to-face interviews were conducted, a large number of which were with next-of-kin as necessitated by inclusion of decedent cases and controls. For example, for females, the number of subject interviews is only 18% for cases (81/460) and 24% (116/366) for controls. The distribution of ages is similar for cases and controls, based on groupings of 10-year intervals.

"ETS exposed" means having ever lived with a household member who smoked regularly. Exposure sources include the home environment during childhood and adulthood but excludes the workplace. There is no mention of whether data on ETS exposure were cross-checked with other interview questions or other sources. No indication was found regarding unmarried females in the sample and how marital status may affect level of exposure to ETS. Some summary information is provided on the distribution of tumors by cell type, but totals include smokers, so they are not reproduced here. The ETS data for females consists of 33 out of 41 (exposed/total) cases and 164 out of 196 controls; for males, the respective figures are 5 out of 11 and 56 out of 90. For the exposure definition given above, the crude odds ratio reported is 0.78 (95% C.I. = 0.34-1.81) for females (direct calculation from the data yields a value of 0.81; Buffler apparently added 0.5 to all cells to compensate for inclusion of no subjects in some cells). Little difference was found when female smokers were categorized by number of years lived with a household member who smoked. No adjusted statistical analysis is provided to account for variables used in matching for the study as a whole, nor is there a test for trend. The authors conclude that no effect of passive smoking is indicated for lung cancer. No attempt is made to evaluate whether exposure to ETS in childhood or adulthood is a factor.

A.4.3. Comments

The potential relationship between ETS exposure and lung cancer risk was not a principal issue in the design of this study. As described in the abstract, and more fully in the study description above, other potential etiologic factors were of more central concern. There are several limitations regarding the study's contribution to the epidemiologic evidence on ETS exposure and lung cancer risk. For example, the interview question on exposure to ETS is not very specific. "Having lived with a household member who smoked regularly" does not distinguish between exposure in childhood and in adulthood, between substantial and only light exposure, or between short-term and long-term exposure. One might expect a high percentage of persons to qualify as "exposed" under such a broad definition, and that is what the study demonstrates: 84%

250103213 6

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

of the controls are classified as exposed. With such a high percentage, both cases and controls may include a number of subjects who have experienced very light exposure to ETS. Another concern in this study is the use of decedent subjects. The majority of both male (86%) and female (82%) cases in the study (including smokers) were deceased. Consequently, a very high percentage of interviews was by proxy (82% of cases and 76% of controls).

This study was conducted in a region with a significantly higher age-adjusted mortality rate for lung cancer than for the United States in general. For all ages combined, the overall excess lung cancer mortality in the Texas study area is approximately 30% to 40% and is considerably higher for some age groups, according to the article. This was the apparent motivation for the study, with emphasis on important occupational and industrial exposures for residents of the Texas coastal area, including those associated with shipbuilding and repair, chemical and petrochemical manufacturing, petroleum refining, construction, and metal industries. If these nonsmoking factors affect the incidence of lung cancer, then they may be confounding the attempt to detect an effect from passive smoking. Appropriate statistical methods need to be applied to adjust the effect of each risk factor for the others.

Other factors may affect the ETS analysis also. Harris County, which is frequently addressed in the article in distinction to the other five counties, was apparently added to the study later (case ascertainment began 1 year later there and included only females; 10 of the 11 hospitals that did not participate are in Harris County). Consequently, there are some regional differences in the study as well as ethnic and racial differences (white and Hispanic). Although the authors took care to match controls on these and other factors, the matching only applies to the whole study (91% and 97% of male and female cases, respectively, are classified as having smoked regularly), not to the ETS subject group specifically, and there is no adjustment for these factors in the analysis. This potential confounding, the insensitive indicator of ETS exposure, and the large use of decedent cases and proxy responses limit the value of this study toward detecting any health effects associated with passive smoking.

A.5. BUTL(Coh)

This study was undertaken to explore the role of active and passive smoking in Seventh-Day Adventists in California. Subjects were participants in a larger prospective cohort study of factors affecting health in Adventists.

In 1974 the Adventist Health Study was initiated with the purpose of investigating the associations of a number of lifestyle and nutritional factors with morbidity and mortality in California Seventh-Day Adventists. Registered Adventist households were identified by

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

contacting the clerks of all 437 California Adventist churches. A basic demographic questionnaire sent to all households received a response rate of 58%. In 1976, all subjects aged 25 or older in 1974 were asked to complete a lifestyle questionnaire that included many demographic, medical, psychological, and dietary variables. Over two-thirds of the targeted subjects responded. From the non-Hispanic whites among these respondents, Butler and his colleagues drew two cohorts. One consisted of 22,120 spouses married and living together at the time of completion of the lifestyle questionnaire in 1976 ("spouse pairs") and the other of 6,467 individuals participating in an Adventist Health Smog Study of air pollution and pulmonary disease (the "ASHMOG" cohort); about two-thirds of the ASHMOG cohort was also included in the spouse-pairs cohort.

Subjects received annual forms for self-reporting of hospitalizations in the past year. Medical records relating to reported hospitalizations were then reviewed. Mortality was traced in four ways: linkage with California Death Certificate and National Death Index Systems, church clerk notification of deaths entered in church records, and follow-up of hospitalization history form responses (or nonresponses). Underlying and contributing causes of death were obtained from death certificates. Death certificates were obtained for all reported fatalities.

For the spouse-pairs cohort, subjects were considered unexposed to ETS if their spouses were either never-smokers *or* ex-smokers baptized into the Adventist church—which proscribes tobacco usage—before marriage. Those whose spouses were ex-smokers with less than 5 years of total smoking were also considered unexposed. All other subjects with ex- and current smoker spouses were classified as exposed.

Incidence rates were calculated using person-years. In the spouse-pairs cohort, age-adjusted lung cancer mortality rates for females married to past or current smokers were higher than those for female spouses of never-smokers, yielding relative risks of 1.94 and 2.47 for past and current smokers, respectively. Comparison of wives with ever- versus never-smoking husbands yielded a relative risk of 2.0. The same age-adjusted relative risk resulted when analyses were restricted to the 9,207 never-smoking females included in the spouse pairs. Virtually identical risk estimates resulted from both Mantel-Haenszel and Maximum Likelihood analyses. None of the relative risks was statistically significant at the 5% level.

In the ASHMOG cohort, the relative risk of lung cancer adjusted for age and past smoking status among females was 1.16 for women who had lived with a smoker for at least 11 years compared with women who had not lived with a smoker; no difference was observed for women who had lived for less than 11 years with a smoker, although this group was only one-tenth as large as the others. A similar pattern was seen among males who had lived for at least 11 years with a smoker, with an adjusted relative risk of 1.17.

2501032138

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

In the spouse-pairs cohort, age-adjusted rates of smoking-related cancers (excluding lung cancer) were only slightly higher among nonsmoking females married to smokers than among nonsmokers (RR = 1.06); the relative risk rose to 1.22 when lung cancers were included.

In the ASHMOG cohort, age-adjusted rates using conditional maximum likelihood analysis for all smoking-related cancers were higher among males who lived with a smoker (RR = 1.45 for 1-10 years; 1.74 for 11+ years) or worked with a smoker (RR = 2.62 for 1-10 years; 1.47 for 11+ years). Among females, in contrast, only one (at RR = 1.03) of the four exposed categories had a higher rate than the nonexposed groups.

All lifestyle questionnaires were administered anonymously, thus reducing the potential for inaccurate responses caused by fear of discovery; respondents to the special supplemental ASHMOG questionnaire were assured of confidentiality but not anonymity.

Although causes of death were obtained from death certificates, review of medical records revealed histological confirmation in 99% of the primary malignancies reported among the spouse-pairs cohort. Thus, substantial misclassification of lung cancer deaths is unlikely. Subsequent study of patients discharged from 1 of the 11 participating Adventist medical centers over a 6-month period indicated that under 2% of study participants failed to report their hospitalizations; serious underascertainment of cases thus also seems unlikely. Losses to follow-up by study's end totaled only 1.2% of the original study cohort—a very low rate.

Comparing the results of the 1976 questionnaire with those of a supplemental questionnaire given to ASHMOG subjects in 1987, 4.7% of male smokers now reported themselves as "never-smokers" and 1.4% of never-smokers now reported themselves as nonsmokers. Concordance of female responses was even higher. This concordance of responses does not necessarily imply the degree of *accuracy* of responses, only their reliability.

Comparison of responses to the 1987 questionnaire by females revealed that about 6% of those previously classified as not having a smoking spouse now reported having had one; the converse was also true for 6% of the women. These data indicate a mild nondifferential misclassification of exposure, which would push results toward the null.

Information is available on a large number of variables of possible interest as potential confounders or risk mediators. Unfortunately, the modest number of total lung cancer deaths among females in the spouse-pairs cohort (8) or among both sexes in the ASHMOG cohort (13) discourages attempts to control for other potential confounders in addition to age in the analyses. Separate consideration of the association between variables other than passive smoking and age-adjusted lung cancer mortality among women indicated a high relative risk (RR > 4) for spousal blue collar occupation. No other variables produced nearly as strong or consistent an association;

05/15/92
2501032139

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

in fact, the only other consistent association was a relative risk of 1.3 to 1.6 for nonrural status. Unfortunately, no breakdown of blue collar spousal status by exposure groups was presented.

By virtue of its basic design, the inherent minimization of sources of confounding provided by its study population and the level of information available regarding potential confounders, and other sources of bias, the Butler study has many of the key ingredients to produce convincing results. Unfortunately, this potential goes largely unrealized because of the low number of outcome events occurring during the follow-up period, which for the most part renders stratification or control for multiple factors simultaneously impractical; even stratification by several age or exposure levels produces unstable results.

Nevertheless, the findings of this study are quite consistent with the hypothesis that ETS exposure of nonsmokers is associated with mildly elevated lung cancer, (active) smoking-related cancer, and ischemic heart disease mortality. Insofar as the study data allow for consideration of potential misclassification and confounding effects, neither misclassification nor confounding can account for the observed association. Because of the limited number of outcome events, several possible confounding factors could not be definitively or adequately addressed in the analyses and the observed associations were not statistically significant, the study's findings must be viewed as suggestive but not of themselves convincing.

A.6. CHAN

A.6.1. Author's Abstract

(*Note:* This study is described in two sources, both of which were used for the description below. Chan et al. [1979] is the more complete description, but it contains considerable attention to active smoking as a cause of lung cancer. Chan and Fung [1982] is a condensed version that specifically addresses nonsmokers. The abstract given here is for the 1979 article. No abstract is provided in the 1982 source.)

"Bronchial cancer is a disease of high and increasing annual incidence in Hong Kong, especially in women, whose age-specific death rates from this cause are amongst the highest in the world. A case-control study of the relationship of bronchial cancer with smoking was carried out during 1976-77, taking particular note of the histological type of the tumour. Two hundred and eight male and 189 female patients were interviewed, covering about half the total number of cases of bronchial cancer registered as dead from the disease in Hong Kong during the period of survey. The association with smoking was more evident in males than in females, and in squamous and small-cell types, as a group, than in adenocarcinoma. Forty-four per cent of the women with bronchial cancer were non-smokers, their predominant tumour being

2501032140

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

adenocarcinoma, and in them no association could be detected with place of residence or occupation. There was no strong evidence of an association with the use of kerosene or gas for cooking; 23 did not use kerosene. The cause of the cancer in these nonsmoking women remains unknown."

A.6.2. Study Description

(*Note:* This description is primarily based on Chan et al. [1979]. Chan and Fung [1982] are cited when used as a reference.)

This study is the earliest of four from Hong Kong that consider ETS exposure as a potential etiologic factor for lung cancer incidence in nonsmoking women. Here, however, that objective is secondary to evaluation of the relationship of bronchial cancer with active smoking.

In the whole study, target cases are the lung cancer patients, male and female, in five hospitals in Hong Kong during 1976-77 that were willing and able to be interviewed. Controls are patients of the same general age groups from the orthopedic wards of the same hospitals as the cases. No specific diseases are excluded. Cases are incident and control sampling is density. The candidate sample size is 208 (189) male (female) cases and 204 (189) male (female) controls. Attrition from selection or follow-up is not reported but appears high. Subjects were personally interviewed, as possible. About half of the estimated number of lung cancer cases diagnosed in Hong Kong during the study period were actually interviewed. Some patients were too ill to answer questions, and more than expected were treated elsewhere than in the hospitals covered. No interviews with next-of-kin were obtained for the cases interviewed.

The ETS subjects (never-smokers) alone include 84 (2) female (male) cases and 139 (30) female (male) controls. The age distribution of the female cases (controls) is, by percentage, as follows: age less than 40, 7 (5%); ages 40 to 49, 15 (15%); ages 50 to 59, 23 (30%); ages 60 to 69, 23 (22%); and age 70 or more, 32 (28%). Cases with a histological diagnosis were reviewed and verified by reexamination of the pathological specimens. In the absence of a histological specimen, cytological diagnosis was accepted. In some cases, on histological grounds, secondary adenocarcinoma was suspected, and a few cases were rejected after detailed examination of the clinical records. Of the cases, 46 (55%) were diagnosed by histology, 23 (27%) by cytology, and 15 (18%) by radiology and clinical means. Diagnoses by cell type were as follows: squamous or small cell, 19 (22%); adenocarcinoma or large cell, 40 (48%); others and unspecified, 25 (30%). Of the unspecified, 15 had no histological or cytological verification.

ETS subjects are never-smokers. Classification of a subject as exposed or unexposed to ETS is based on the response to these questions: (1) If you do not smoke, have you been exposed

250103214

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

to cigarette smoke from other people at home or at work? (2) Does your husband/wife smoke? (If "yes," how many cigarettes per day?) (The first question is included in Chan et al., 1979. The second one is from a communication of Linda C. Koo.) No information is reported on the distribution of tumors by central and peripheral location.

The ETS data on females based on question 1, above, consists of 50 out of 84 (unexposed/total) cases and 73 out of 139 controls. The authors state that "this is a rather subjective approach to the problem." No statistical estimates are provided; our calculation of the crude odds ratio is 0.75 (95% C.I. = 0.43-1.30). No clear conclusion is drawn regarding the potential relationship between ETS exposure and lung cancer occurrence, but the authors imply that no connection was found (which the odds ratio and confidence interval amply support). The authors found no particular occupation as being dangerous. Their findings also do not support air pollution as a factor, and they provide no strong evidence that cooking with various types of fuel is relevant.

A.6.3. Comments

Although data on spousal smoking were collected along with an indication of the number of cigarettes smoked per day, they are referred to only in the 1982 article, where the authors note without further elaboration that more nonsmoking cases have nonsmoking spouses. It is reported that answers to the question, "Are you exposed to the tobacco smoke of others at home or at work?" gave no indication that other people's smoking was a risk factor for lung cancer in nonsmokers, with 40.5% of cases and 47.5% of controls answering yes to this question. Why the data for spousal smoking are not given and analyzed is unknown. The question about general ETS exposure combines sources in the household and workplace and refers only to current exposure without a measure of duration, which would likely affect any risk associated with passive smoking.

Although it is reported that cases and controls are similar in age, occupation, and other characteristics, comparability is questionable. The article cites a criticism of the whole study (including smokers) for use of orthopedic patients as controls, on the basis that some patients may be hospitalized with smoking-related diseases (e.g., osteoporosis). It was found that the controls smoke more than a group representative of the population of Hong Kong. This would create a bias toward negative association. Although these comments refer to smoking habits, they suggest the potential for selection bias of controls that may extend to nonsmoking controls as well.

It is noted, also, that there are more cases from Hong Kong Island than would be expected from the population distribution of Hong Kong as a whole, possibly due to more success

25010321H2

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

contacting cases in Hong Kong Island than in Kowloon. The authors caution about reaching any conclusion about the distribution of cases within Hong Kong as a whole. The failure to follow up on patients who were eventually treated at other hospitals or were too ill to be interviewed is, of course, a potential source of bias itself.

Other differences are apparent between cases and controls. Among nonsmokers, a higher percentage of cases than controls (1) are Cantonese (81 vs. 70) or (2) have ever cooked with kerosene (73 vs. 60). It is speculatedthat the Cantonese diet, high in nitrite or nitrate content, may be a factor in lung cancer incidence (Chan and Fung, 1982). More broadly, these comparisons between cases and controls indicate differences in ethnic composition, lifestyle, and socioeconomic status that are difficult to assess.

In summary, ETS subjects are not matched in the design, and an adjusted statistical analysis is not conducted. Consequently, potential sources of bias and confounding are not controlled. There is substantial basis to question the comparability of cases and controls, as described above. Data quality is suspect because confirmation of primary lung cancer was limited and cases were missed because patients were too ill to be interviewed personally or were eventually treated at another hospital. Also, the question posed to subjects for classification as exposed or unexposed to ETS is sufficiently general to invite subjective response. Overall, methodological shortcomings hamper interpretation of this study's findings, rendering its conclusions questionable.

The finding that spousal smoking appears to be more frequent in controls, mentioned in the 1982 report, is noted to be at variance with the Hirayama study, which may have motivated the authors to conduct this secondary analysis of ETS exposure using their previously collected data. Whatever the motivation, the original study is rather limited as a source to evaluate passive smoking. Overall, this study does not reflect as much care and attention to detail as would be useful, limiting its value for assessing ETS exposure and lung cancer.

A.7. CORR

A.7.1. Author's Abstract

"Questions about the smoking habits of parents and spouses were asked in a case-control study involving 1,338 lung cancer patients and 1,393 comparison subjects in Louisiana, USA. Nonsmokers married to heavy smokers had an increased risk of lung cancer, and so did subjects whose mothers smoked. There was no association between lung cancer risk and paternal smoking. The association with maternal smoking was found only in smokers and persisted after controlling for variables indicative of active smoking. It is not clear whether the results reflect a biological

2501032143

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

effect associated with maternal smoking or the inability to control adequately for confounding factors related to active smoking. This preliminary finding deserves further investigation."

A.7.2. Study Description

This study was conducted in Louisiana to investigate the relationship of smoking habits of parents and spouses to lung cancer occurrence. Results of the study were published in 1983; some clarifying details regarding study methodology were supplied in a 1984 paper addressing only the effects of active smoking. The accrual period is not stated; cases are probably a mixture of prevalence and incidence, and controls are cumulatively sampled. ETS subjects constitute a small portion of the whole study, which includes active smokers.

Cases consist of patients diagnosed with primary lung cancer, exclusive of bronchioalveolar carcinoma, from participating hospitals in several Louisiana parishes (counties), predominantly in the southern part of the state. A total of 302 female and 1,036 male cases and an equal number of controls are included in the whole study. Controls were selected from other patients, excluding those diagnosed with emphysema, chronic bronchitis or obstructive pulmonary diseases, or certain cancers (laryngeal, esophageal, oral cavity, and bladder). They were matched to cases on hospital, age (± 5 years), sex, and race. Information about active and passive smoking was obtained by interview (presumably face to face and unblinded), with responses obtained from next-of-kin in 24% of cases and 11% of controls; no information on refusals is provided. ETS subjects were identified by exclusion of individuals who had ever smoked or had never been married, which eliminated 279 female and 1,026 male cases. Removal of subjects with no spousal smoking data eliminated one additional female and two male cases, leaving 22 female and 8 male cases. Similarly, a total of 1,080 men and women were excluded from controls. No demographic comparisons are given, either for the whole study or for the ETS subjects alone, nor is the number of proxy responses provided for the ETS subjects. Histological confirmation was obtained for 97% of cases in the whole study, including ever-smokers.

"ETS exposed" is used in two ways, depending on the analysis given: (1) the spouse has smoked at least 1 pack-year of cigarettes or (2) the spouse currently smokes. Units of exposure are pack-years and current consumption is in cigarettes per day for (1) and (2), respectively. ETS exposure in childhood means that at least one parent smoked during most of the subject's childhood. Types of tobacco smoking other than cigarettes (e.g., cigars and pipes) are referenced indirectly in regard to interview questions but are not included in the data analysis. Other sources of exposure, either at home or in the workplace, are not considered. Never-married women are excluded from ETS analysis, but no information is given on the number of nonsmoking widows

25010321HH

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

and divorcees and how they were handled with regard to ETS exposure. Adenocarcinoma accounts for 54% of lung cancers in nonsmoking women, compared to 22% in women who actively smoke. No further histological breakdowns are provided.

For the main analysis of spousal smoking, exposure constitutes one or more pack-years of spousal cigarette consumption. ETS-exposed subjects include 14 (61) of 22 (133) female cases (controls) and 2 (26) of 8 (180) male cases (controls). These data yield a crude odds ratio of 2.07 (95% C.I. = 0.81-5.25) for females (confidence interval was calculated by reviewers). Among females, stratification by 0, 1 to 40, and 41 or more pack-years of exposure yields odds ratios of 1.0, 1.18, and 3.52, respectively, with the highest exposure category being statistically significant at $p < 0.05$. No adjusted results are presented. It is, however, reported that analyses based on current daily spousal cigarette consumption produced very similar results to the pack-year analyses. In addition, it is reported that neither exclusion of proxy interview data nor restriction to same-race subjects significantly alters the results. Analysis of parental smoking during childhood embraces the combined population of smokers and nonsmokers, adjusting for smoking status by logistic regression. Maternal smoking is associated with significantly increased estimated risk of lung cancer (OR = 1.38, $p < 0.05$) but paternal smoking is not (OR = 0.83). No association was noted among nonsmokers alone, but the authors note that small numbers preclude adequate analysis of this group.

A.7.3. Comments

The study entails a major multicentric effort to assemble hospital-, age-, race-, and sex-matched lung cancer cases and controls from Louisiana hospitals. Its use of trained local interviewers familiar with the region's culture increases the probability of obtaining accurate interview data for the nearly 3,000 subjects involved. Exclusion of active smokers to assess ETS exposure, however, exacts a toll on the study's power and validity. Because the initial matching of cases and controls did not include smoking status, the ETS subjects are unmatched in the analyses of spousal and parental smoking. This potential problem is not addressed by the authors. The lack of any demographic information on cases and controls leaves the comparability of these groups uncertain.

The potential problem of misdiagnosis of primary lung cancer is minimized by the high rate (97%) of histological case confirmations. Eligibility criteria for controls were intended to exclude smoking-related diseases. Some 15% of the controls had cardiovascular disease, however, which has been associated with both active and passive smoking. The authors also speculate that the inclusion of adenocarcinoma, reportedly less smoking-associated than other lung cancers, may

2501032145

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

have diluted the significance of their results, but they do not present analyses using their extensive histological data to assess this question.

Restriction of the spousal smoking analysis to ever-married individuals eliminates potential confounding by differences between lifelong single and married individuals. Stratification by gender controls for any sex-related differences. Both race and proxy interview were reported to have no effect on the spousal smoking results, and the spousal smoking association was still observed after division of women into over and under 60 years of age. A small number of nonsmoking ever-married cases (8 males and 22 females for this study) hampers efforts to control statistically for confounders; nonetheless, direct adjustment for age and race is needed. There are other potential confounders not controlled for, such as socioeconomic status, diet, and other sources of smoke exposure.

It is concluded that females married to heavy smokers have an increased risk of lung cancer. A significant increase in risk for nonsmokers was found from maternal but not from paternal smoking in childhood. The results for childhood exposure, however, use statistical methods to adjust for the presence of active smokers instead of removing the data for them prior to analysis. This gives the *appearance* of increasing an otherwise small sample size (the ETS subjects alone) to attain significance, at the risk of biased results. The potential for bias in all of the analyses, which could be in either direction and may or may not be of consequence, needs to be kept in mind when using this study's results.

A.8. FONT

A.8.1. Author's Abstract

"The association between exposure to environmental tobacco smoke (ETS) and lung cancer in female lifetime never-smokers was evaluated using data collected during the first three years of an on-going case-control study. This large, multi-center, population-based study was designed to minimize some of the methodological problems which have been of concern in previous studies of ETS and lung cancer. Both a cancer control group and a population control group were selected in order to evaluate recall bias. A uniform histopathologic review of diagnostic material was conducted for case confirmation and detailed classification. Biochemical determination of current exposure to tobacco and screening of multiple sources of information to determine lifetime nonuse were employed to minimize misclassification of smokers as nonsmokers.

A 30% increased risk of lung cancer was associated with exposure to ETS from spouse, and a 50% increase was observed for adenocarcinoma of the lung. A statistically significant positive trend in risk was observed as pack-years of exposure from spouse increased, reaching a relative

250103146

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

risk of 1.7 for pulmonary adenocarcinoma with exposures of 80 or more pack-years. The predominant cell type of the reviewed, eligible lung cancer cases was adenocarcinoma (78%). Results were very similar when cases were compared to each control group and when separate analyses were conducted for surrogate and personal respondents. Other adult-life exposures in household, occupational, and social settings were each associated with a 40% to 60% increased risk of adenocarcinoma of the lung. No association was found between risk of any type of lung cancer and childhood exposures from father, mother or other household members."

A.8.2. Study Description

This study was initiated in 1985 in five major U.S. metropolitan areas to investigate the association between exposure to ETS and lung cancer in female lifetime never-smokers. The study was designed specifically to address this issue and includes only never-smokers. The results reviewed are from an interim report, with the completed study expected to encompass an additional 2 years of case accrual.

Patients were English-, Spanish-, or Chinese-speaking female residents 20 to 79 years of age who have never used tobacco, have no prior history of malignancy, and have histopathologically confirmed primary lung cancer. The lung cancers were originally diagnosed at participating hospitals in Atlanta, Houston, Los Angeles, New Orleans, and the San Francisco Bay area, between December 1, 1985, and December 31, 1988. Two control groups were assembled, one from colon cancer patients and the other from the general population, with the same general eligibility requirements as cases. The population control group, consisting of women selected from the general population by random digit dialing and by sampling from Health Care Financing Administration files, were frequency matched on age (< 50, 50-59, 60-69, 70+), with two controls per case. The colon cancer controls were frequency matched to cases by 10-year age groups and by race. The lung cancer group consists of incident cases, but there is no indication whether density or cumulative sampling was employed for either control group. Exposure data were collected in face-to-face, apparently unblinded, interviews.

Extensive efforts were made to include only never-smokers. For cases and colon cancer controls, medical records were reviewed for tobacco use and physicians were contacted as necessary. Eligible cases not previously excluded and all population controls were contacted by telephone to screen for prior use of tobacco (no more than 100 cigarettes smoked or use of any tobacco in any form for more than 6 months). Urinary cotinine was bioassayed to eliminate any misreported current smokers.

2501032147

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A total of 514 eligible cases were identified, of which 83 were not interviewed for unspecified reasons and 2 had urinary cotinine levels consistent with active smoking. Independent histopathologic review by a pulmonary pathologist was performed for 84% (359/429) of the lung cancer cases, resulting in nine exclusions. Only the remaining 420 cases are included in the study. Colon cancers were not reviewed. Of 489 (1,105) eligible colon cancer (population) controls, 131 (311) were not interviewed and 7 (14) were excluded for high urinary cotinine. Proxies were interviewed for 143 (34%) of the lung cancer cases and 35 (10%) of the colon cancer controls, whereas no proxies were used for the population controls.

Cases and the two control groups all have similar age distributions, with the majority of subjects between 60 and 79 (73%, 74%, and 74% of the cases, colon, and population groups, respectively). The proportion of whites is similar across all groups (63-69%), but the control groups contain a somewhat higher proportion of blacks and lower proportion of other minorities, and a little higher percentage of high school graduates (76% and 79% vs. 68%). Cases and controls are comparable by metropolitan size of adulthood and childhood residences and also by annual income.

Four sources of adult ETS exposure are assessed: smoking by (1) spouse(s) and (2) other household members while living with the subject, and reported exposure to ETS in (3) occupational and (4) social settings. Three sources of possible exposure in childhood (up to 18 years of age) are considered: smoking by (1) father, (2) mother, or (3) other household member(s) while living in the subject's home for at least 6 months. Subjects are characterized as ever- versus never-exposed with a subanalysis by tobacco type (cigarette, pipe, or cigar). Years of exposure are also tabulated. In addition, cigarettes per day for spouse and for other household sources and pack-years for spouse(s) are calculated. No checks on exposure (aside from the cotinine screening) are reported.

Adenocarcinoma is the dominant type of lung cancer among study subjects, representing 76% (311/409) of all cases included in the study (with the exception of 11 cases with "review pending") and also 78% (281/359) of all independently confirmed primary bronchogenic carcinomas among those cases. Other cell types include 12% (48/409) large cell, 7% (27/409) squamous cell, 3% (14/409) small cell, and 2% (9/409) other cancers. No data on airway proximity are provided.

The final study population (for this interim report) consists of 420 lung cancer cases, 351 colon cancer controls, and 780 population controls. Exposure to spousal smoking from all types of tobacco is reported for 294 cases, 231 colon cancer controls, and 492 population controls, yielding similar odds ratios (adjusted for age, race, area, income, and education) of 1.28 (95% C.I. = 0.93-

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

1.75) and 1.29 (0.99-1.69) using the respective control groups. Elevated but statistically nonsignificant observed risks are also observed when cigarette, cigar, and pipe exposure are assessed separately, with either control group. Restriction of analyses to the 281 independently reviewed adenocarcinomas results in stronger associations, with adjusted odds ratios of 1.44 (95% C.I. = 1.01-2.05) and 1.47 (1.08-2.01) for all types of tobacco, and increased odds ratios for each type of tobacco as well.

Odds ratios were also calculated for ETS exposure from cigarette smoking alone, with the two control groups combined (the individual results using each control group are entirely consistent). For all lung cancer types combined, the adjusted odds ratios are 1.21 (0.96-1.54) for spousal smoking, 1.23 (0.97-1.56) for other household members, 1.34 (1.03-1.73) for occupational environments, and 1.58 (1.22-2.04) for social exposure, the last two of which are significant ($p < 0.05$ and 0.01, respectively). The corresponding odds ratios for adenocarcinoma cases alone continue to be uniformly higher: 1.38 (95% C.I. = 1.04-1.82), 1.39 (1.05-1.82), 1.44 (1.06-1.97), and 1.60 (1.19-2.14). The odds ratio tends to increase over years of exposure for all carcinomas combined and for adenocarcinoma alone, although not monotonically (without downturns). The tests for upward trend are all significant or suggestive, with p-values ranging from < 0.001 to 0.07 (these p-values are half those reported, which apply to a trend in either direction). Finally, for spousal smoking measured in pack-years, the upward trend is significant for adenocarcinoma alone and for all lung cancers together ($p < 0.005$ and 0.04, respectively).

The authors interpret their findings as evidence of a causal relationship between ETS exposure in adulthood and lung cancer in never-smoking women. In contrast to adulthood, ETS exposure during childhood shows no association with lung cancer, for either all cell types combined or adenocarcinoma alone. Adjusted odds ratios tend to be slightly (but not significantly) below unity for all exposure sources.

A.8.3. Comments

This study is much larger than any other ETS case-control study. Over 400 never-smoking female lung cancer cases were enrolled in just over 3 years, in contrast to the 25 to 75 cases typical of most studies, and two control groups were formed, totaling over 1,200 subjects. Additionally, the cases and controls are drawn from five widely dispersed metropolitan centers in the United States, representing a population of approximately 18.5 million people, about 8% of the U.S. population. This characteristic increases the generalizability of the study and diminishes the potential for bias related to locale.

250103149

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Extensive efforts were made to achieve precision and validity, in evidence throughout the study. Cases and controls are highly comparable. They are frequency matched on age and, for colon cancer controls, on race as well. The distributions of other demographic variables—annual income, childhood residence, and adult residence—are quite similar between cases and both control groups. The control groups contain a little higher (lower) proportion of blacks (Asians and Hispanics) and a higher percentage of high school graduates. These differences, however, should not have influenced the reported associations because all odds ratios are adjusted for race and education.

The use of incident cases reduces the potential for selection bias, and the implementation of two control groups allowed for assessment of potential bias from comparison with cancer patients or the general population alone. The similarity of results obtained from the two control groups suggests little bias from choice of controls.

The use of a multistep procedure to eliminate inclusion of former or current smokers reduces the potential for smoker misclassification as a source of upward bias. As a further safeguard, urinary cotinine was bioassayed for all consenting persons to exclude those likely to be current smokers. This is the only published study we are aware of to implement this precaution. Attention to histopathology is also very thorough. Inclusion of only histologically diagnosed primary carcinoma reduces the likelihood of diagnostic error, which is further reduced by the use of independent histopathologic review of most cases by a single pulmonary pathologist. The study's histopathologic findings bring out two interesting points. First, comparison of cell type diagnoses between hospital and independent reviewers revealed poor concordance for large (56%) and squamous (67%) cell carcinomas, indicating that cell-type-specific analyses for these cancers may be misleading, particularly if all diagnoses are not made by the same pathologist. The histopathologic review also resulted in a net increase of adenocarcinomas from 244 to 281, 78% of the total, a higher proportion than in most but not all other studies. The statistical results were stronger when limited to cases of adenocarcinoma alone.

Exposure information was obtained in the most reliable way, by face-to-face interviews with each interviewer trained and fluent in the subject's primary language. Information for a substantial proportion of lung cancer cases (34%) was obtained from proxy respondents, but fewer proxies were required for colon cancer controls (10%), and none were used for population controls. The use of proxy respondents raises the possibility of information bias, but their exclusion reportedly did not alter the study's findings. The apparent lack of blinding also raises the possibility of interviewer bias, but it is unlikely that such bias (or recall bias, for that matter)

05/15/92

2501032150

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

would restrict its effect to adenocarcinoma. Also, the same relationships hold whether the colon cancer or population controls are used.

Particular attention is paid to all sources of ETS exposure, which is more informative than addressing only spousal smoking, with four sources in adulthood and three in childhood evaluated both individually and in combination. Additionally, subjects are counted as exposed to the ETS of a spouse or other household smoker only *while living with* the source, giving a more accurate account of exposure than simply determining whether a spouse or household member ever smoked. Consequently, the measures of ETS exposure are more specific by source, and probably more accurate, than in most studies. This reduces bias toward unity in the odds ratio arising from poor distinction between exposed and unexposed subjects. Still, further accuracy might have been achieved by stipulating that smoking must occur in the subject's household or presence, but this is a minor point.

Most of the standard potential confounders—age, race, geographic area, income, and education—are adjusted for in all analyses and thus can be ruled out as sources of the observed results. Although information on diet, occupational exposures, and "other exposures of interest" were collected, these factors are not addressed in this interim report. Thorough treatment of the issue of potential confounding by these factors will presumably be undertaken after subject accrual is finished and published in the completed study.

To summarize, this study was designed specifically and solely to address the topic of ETS as a potential lung cancer risk to nonsmoking women. Several issues were given special attention, such as the potential misclassification of smoking status, histopathologic specificity, recall bias, source of ETS exposure, and potential confounders and other risk factors. Histopathologic specificity has not been convincingly demonstrated in prior studies, and the meaning of "exposed to ETS" has differed widely between studies, even those addressing spousal smoking only. The remaining issues are largely related to controlling potential sources of bias and confounding to enhance validity. The qualitative rigor and completeness of detail in this study is impressive. In addition, it is quite large, which increases precision of estimates and power to detect an association, if it exists. Use of dietary, occupational, and other exposure data in the analyses, along with an additional 2 years of subject accrual, will make the completed study for which this constitutes an interim report even more valuable. As it stands, however, this study is already the largest and most useful case-control study available. Its high quality and the reasonable consistency of the evidence across sources of ETS exposure strongly support an increase in lung cancer incidence associated with passive smoking.

2501032151

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.9. GAO

A.9.1. Author's Abstract

"A case-control study involving interviews with 672 female lung cancer patients and 735 population-based controls was conducted to investigate the high rates of lung cancer, notably adenocarcinoma, among women in Shanghai. Cigarette smoking was a strong risk factor, but accounted for only about one-fourth of all newly diagnosed cases of lung cancer. Most patients, particularly with adenocarcinoma, were life-long non-smokers. The risks of lung cancer were higher among women reporting tuberculosis and other pre-existing lung diseases. Hormonal factors were suggested by an increased risk associated with late menopause and by a gradient in the risk of adenocarcinoma with decreasing menstrual cycle length, with a 3-fold excess among women who had shorter cycles. Perhaps most intriguing were associations found between lung cancer and measures of exposure to cooking oil vapors. Risks increased with the number of meals cooked by either stir frying, deep frying or boiling; with the frequency of smokiness during cooking; and with the frequency of eye irritation during cooking. Use of rapeseed oil, whose volatiles following high-temperature cooking may be mutagenic, was also reported more often by the cancer patients. The findings thus confirm that factors other than smoking are responsible for the high risk of lung cancer among Chinese women and provide clues for further research, including the assessment of cooking practices."

A.9.2. Study Description

This study was undertaken in Shanghai, China, during 1984-86 to explore reasons for the high rates of lung cancer among women in Shanghai. Potential etiologic factors associated with the high occurrence of adenocarcinoma among females in a population where few women smoke cigarettes is of particular interest. Several potential risk factors, in addition to exposure to ETS, are investigated. These are included in the abstract above. Smokers are included in the study as well as nonsmokers.

A special reporting system for lung cancer linked with the area's medical facilities was set up for the study period, integrated with the Shanghai Cancer Registry. Incident cases of lung cancer occurring among 35- to 69-year-old female residents of urban Shanghai from February 1984 to February 1986 were interviewed by trained study personnel. Controls were women selected from residents of the urban Shanghai community by stratified random sampling designed to mimic the age distribution of Registry-reported lung cancer cases during 1980-81. It is not clear whether cumulative or density sampling was employed.

2501032152

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Face-to-face interviews were conducted with 672 cases and 735 controls. No cases refused to be interviewed, but 93 died before interview and were therefore excluded; it is not mentioned whether there were any refusals among potential controls. Nonsmokers composed 436 of the cases and 605 of the controls. In the total subject population, distribution of age, education, and marital status between cases and controls is described as similar, except for a larger proportion of controls (32% vs. 20%) in the oldest age group (65-69 years). The age distribution in the ETS population alone is not described.

ETS exposure is based on living with a smoker. For general exposure in childhood or adulthood, exposed subjects are those who ever lived with a smoker. For spousal smoking alone, however, women are ETS exposed only if they lived with a smoking husband for *at least* 20 years. General ETS exposure sources include all household members but not coworkers. Verification of exposure data was not mentioned. Based on the reported exposure criteria, widows and divorcees would have been included in the spousal smoking data set, whereas never-married women would have been excluded.

For ETS subjects, 246 (375) cases (controls) from the total of 672 (735) cases (controls) are included in Table II of the article that lists the number of cases and controls by number of years lived with a smoking husband. Presumably the 190 cases and 230 controls not included in the table are unmarried (or never-married) and do not include women married and living with a nonsmoker; no explanation is provided in the article.

Among nonsmoking women included in Table II, 189 out of 246 cases and 276 out of 375 controls had lived with a smoking husband for at least 20 years. These subjects were divided into exposure categories of 20 to 29, 30 to 39, and 40 or more years for comparison with the "unexposed" (< 20 years spousal smoking) subjects. The authors present no unadjusted analyses, but calculations from their raw data yield an overall odds ratio of 1.2 and stratum-specific odds ratios of 1.2, 1.3, and 1.1 for 20 to 29, 30 to 39, and 40 or more years of exposure, respectively. Age and education-adjusted odds ratios increase with the number of years exposed: 1.1 (95% C.I. = 0.7-1.8) for 20 to 29 years, 1.3 (0.8-2.1) for 30 to 39 years, and 1.7 (1.0-2.9) for 40 or more years. The authors report an odds ratio of 2.9 (1.0-8.9) for squamous and oat cell cancer for 40 years of exposure or less but present no other type-specific results.

Information on cell type is available for the 542 (81%) study cases diagnosed by histology or cytology; the rest of the cases were diagnosed by radiological or other means. Diagnostic evidence was reviewed by a team of pathologists and clinicians. For the lung cancer cases histologically typed, adenocarcinoma (61%) greatly predominates, followed by squamous (22%),

250103215 3

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

small cell (6%), and other (11%) types. No breakdowns of tumor type are provided for the ETS group.

The authors conclude that ETS may account for some, but probably few, of the cancers among nonsmokers, because there was little or no association with ever having lived with a smoker. Among nonsmoking women married to smokers, however, there was an upward trend in risk associated with increasing years of exposure. This latter finding is consistent with reports in other parts of the world. Little evidence was found to implicate the type of fuels used for cooking in lung cancer risk; occupational factors did not appear to be important, nor did familial tendency to lung cancer. Our data suggest, however, that prior lung diseases, hormonal factors, and cooking practices may be involved. Most provocative is the association with cooking oil volatiles, and further investigations are needed to evaluate their contribution to the high lung cancer rates among Chinese women in various parts of the world.

A.9.3. Comments

The number of ETS subjects for analysis is relatively large. Unfortunately, the study is unmatched, with no demographic breakdown of the cases and controls, either for the whole study or for the ETS subjects alone. Controls were selected to make their age distribution similar to that expected for cases in the whole study, but the similarity may not apply to ETS subjects alone. Consequently, there is little basis for evaluating the comparability of cases and controls. Age and education were adjusted for in the analyses, which has some compensatory value.

The use of direct interview with all subjects without reliance on proxies to gather exposure information should enhance the validity of the exposure comparisons. On the other hand, the possible use of unblinded interviewers could have biased results. In light of the lack of association noted for passive smoke exposure as a child or adult, however, it is unlikely that such a bias produced the observed association between spousal smoking and lung cancer. For evaluation of spousal smoking, the reference group can hardly be classified as "unexposed" to spousal smoking because it includes women who lived with a smoking husband for up to 20 years. The investigators probably selected the cutoff level of exposure for their spousal smoking reference group to balance the numbers in each exposure category, as a practical matter. The reference group contains an undisclosed number of women who may have been exposed to spousal smoking for many years, potentially creating a substantial bias toward the null hypothesis (no association between ETS exposure and lung cancer). Consequently, the odds ratios may be biased downwards. The relative comparison across years of spousal smoking, however, is not affected. An increasing trend in the odds ratio was observed, but no statistical test for trend is cited. In a similar vein, it

250103215

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

appears that active smokers *may* have been included in the data analysis of overall ETS exposure. That factor, in combination with the use of ever- versus never-exposed classifications without regard to degree or duration of ETS exposure in the analyses, may have reduced the likelihood of detecting any positive association that may exist.

The study appears to have focused on potential risk factors other than ETS. Unfortunately the effects of these other factors on the ETS results were not explored, even though many of these appeared to be stronger risk factors than passive smoking. Some potential confounding factors, such as age and education, *were* adjusted for in all analyses. Control for education should in turn produce a degree of adjustment for factors related to socioeconomic status (e.g., dwelling size and quality of diet).

Overall, the study presents evidence of a mild duration-dependent association between lung cancer and spousal smoking that skirts statistical significance. Several sources of misclassification bias are possible, but most would tend to bias the odds ratio downward. The study was not, however, specifically designed to evaluate the ETS-lung cancer hypothesis. Information was collected and analyzed on a number of other potential risk factors, but none of these besides age and education were considered as potential confounders. Coupled with other limitations, this omission reduces the weight of the study's results with regard to ETS, although they support an increase in lung cancer risk with spousal smoking.

A.10. GARF (Case-Control)

A.10.1. Author's Abstract

"In a case-control study in four hospitals from 1971 to 1981, 134 cases of lung cancer and 402 cases of colon-rectum cancer (the controls) were identified in nonsmoking women. All cases and controls were confirmed by histologic review of slides, and nonsmoking status and exposures were verified by interview. Odds ratios (OR) increased with increasing number of cigarettes smoked by the husband, particularly for cigarettes smoked at home. The OR for women whose husbands smoked 20 or more cigarettes at home was 2.11 (95% C.I. 1.13, 3.95). A logistic regression analysis showed a significant positive trend of increasing risk with increasing exposure to the husband's smoking at home, controlled for age, hospital, socioeconomic class, and year of diagnosis. Comparison of women classified by number of hours exposed a day to smoke in the last five years and in the last 25 years showed no increase in risk of lung cancer."

2501032155

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.10.2. Study Description

This study was undertaken in New Jersey and Ohio to investigate the relationship of involuntary smoking to primary lung cancer. All data were collected specifically for this study, and only nonsmokers were included as subjects. Cases are the lifelong nonsmoking women histologically diagnosed with primary lung cancer during 1971-81 in four participating New Jersey and Ohio hospitals. Controls selected from patients with colorectal cancer were matched 3 to 1 to a case on hospital and age (± 5 years). Subjects were not restricted to incident cases, and controls were apparently cumulatively sampled. Exposure data were obtained by blinded, face-to-face interviews with subjects or their relatives.

A total of 1,175 female lung cancer cases were initially identified from medical records. Exclusion of women found to be current or former smokers or not to have histologically verified primary lung cancer eliminated 1,041 of the identified cases, leaving 134 ETS subjects. Interviews were conducted with patient, spouse, or child in about 75% of the subject population, whereas the rest were conducted with another relative. The age distributions of cases and controls are nearly identical.

ETS exposure includes pipe and cigar use as well as cigarette smoking. Three sources of passive smoking are considered, which will be referred to as follows: "exposure to husband's smoke" means having a husband *or* other related cohabitant who smokes more than occasionally, either (1) anyplace or (2) at home; "general exposure" applies to the smoke of others at home, work, or otherwise who have smoked more than occasionally during the past (1) 5 years or (2) 25 years; and "childhood exposure" refers to experiencing ETS from any source during childhood. Husband's smoking is quantitated as cigarettes per day and years smoked; general exposure is given as average hours per day; and childhood exposure is treated as a dichotomous variable. Only 57 percent of the cases were women living with a husband at the time of diagnosis. No checks on exposure status are described, and no classification of subjects by marital status was implemented. Adenocarcinoma (87) predominates among lung cancer cases, followed by large cell (21), small cell and miscellaneous (15), and squamous cell cancer (11); no data on airway proximity are provided.

Ninety of 134 cases were exposed to husband's (or other relatives') smoking at home, compared to 245 of 402 controls, giving a crude odds ratio of 1.31 (reported 95% C.I. = 0.99-1.73; C.I. calculated by reviewers is 0.87-1.98). For husband's smoking of 20 or more cigarettes per day, the highest exposure category, the odds ratio increases to 2.11 (1.13-3.95). Husband's smoking averaged 11.5 cigarettes per day for the exposed subject. For husband's smoking anyplace, 91 of 134 cases and 254 of 402 controls were exposed, giving a crude odds ratio of 1.23 (0.94-1.60). At the highest exposure category, 40 or more cigarettes per day, the odds ratio is 1.99

2501032156

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

(1.13-3.50). Cigar and pipe smoking alone yields odds ratios of 1.17 and 1.13 for husband's smoking at home and anyplace, respectively. There are statistically significant trends for both husband's smoking at home and for smoking anyplace when measured by cigarettes per day, but not when evaluated by number of years smoked. The odds ratio for ETS exposure from husband's smoke, both total and at home, is calculated by source of interview respondent for the categories of "self," "husband," "daughter or son," and "other." It is readily apparent that the excess risk is attributable to "daughter or son," with some contribution from "other." *None* of the excess risk is attributable to "self" or "husband."

General smoke exposure also shows an association with lung cancer. Exposure over the past 5 and past 25 years yield odds ratios of 1.28 (0.96-1.70) and 1.13 (0.60-2.14), respectively. The odds ratios do not increase with increasing level of exposure, however, and none of the associations is statistically significant. No association was found between childhood smoke exposure and lung cancer (OR = 0.9, 0.74-1.12). When the odds ratio is calculated by source of respondent, "other" and "self" account for the excess risk when smoking for 5 years is the measure; for 25 years of smoking, "other" and "daughter or son" account for the excess risk.

Stratification by cell type reveals that husband's smoking is much more strongly associated with squamous cell (OR = 5.00, both for smoking at home and anyplace) than adenocarcinoma (corresponding ORs = 1.33 and 1.48); no association with other cell types was detected. Stratification by age and socioeconomic status suggests little effect of these variables on the results. The results, however, appear to be sensitive to whether the interview data were obtained from the subject or a surrogate (offspring, relative, etc.), as noted above.

A logistic regression analysis including adjustment for age, hospital, socioeconomic status, and year of diagnosis was undertaken for passive smoking. Cigarettes per day of husband's at-home smoking is significantly associated with lung cancer, with an estimated relative risk of 1.7 at exposure of 20 cigarettes per day compared to none. In contrast, husband's smoking outside the home is *not* significantly associated with lung cancer, although the estimated relative risk is 1.26 for 20 cigarettes per day. General smoke exposure is not significantly associated with lung cancer, for either the 5 years or past 25 years of exposure. Adjustment for type of respondent reportedly had no significant effect on the logistic regression results.

A.10.3. Comments

The abundance of nonsmoking cases (134) and controls (402) in this study relative to most ETS studies gives it above-average statistical power. Comparability of cases and controls appears good based on their very similar age distributions, matching on hospital and age, and restriction to

250103157

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

nonsmokers. But the lack of further demographic comparisons means that divergence on some other factor(s) cannot be ruled out.

A major difficulty in this study, however, arises from the extensive use of proxy respondents. Only 12% (16 of 134) of the case interviews were with the patient. In the stratified analysis, it was found that the husband's smoking at home is positively associated with lung cancer only when the smoking information is provided by a son or a daughter rather than by the patient or her husband. This leads to two possibilities. Either the son or daughter claimed that the patient's husband smoked when he actually did not, thereby shifting cases from the nonexposed to exposed category and increasing the odds ratio, or the patient or her husband claimed that the husband did not smoke when actually he did, thereby shifting cases from the exposed to nonexposed category and depressing the odds ratio. In general it is thought more likely that true smokers are misclassified as nonsmokers more often than true nonsmokers are misclassified as smokers (see, for example, Lee, 1986, and Machlin et al., 1989). Also, Machlin indicates that proxies tend to misclassify smokers no more often than smokers themselves do. Thus, it may be that the son or daughter data are better than the self or husband data. On the other hand, the difference among the reporting sources may be due only to chance because the results in JANE on self or proxy reports are quite the opposite of those in this paper, with the proxy reports (in this case including the spouse) leading to lower odds ratios than the self-reports.

Another possible problem with this study is the use of colon and rectal cancer cases as controls on the theory that these diseases are not smoking related. A recent paper, Zahm (1991), notes that associations have been found between smoking and these cancers. If these associations carry over to passive smoking, they might bias the result either higher or lower.

In general, the detailed results from the stratified analysis in Table 6 of the paper exhibit considerable variation, probably caused by chance. Hence, the overall results in Table 5 of the article, where all the cases and controls are used, may be the most reliable. They indicate an odds ratio of 1.31 (1.24 after adjustment for smoker misclassification bias in the body of this report) for exposure to all types of husband's smoking at home.

The study's exposure assessment methodology is strengthened by the attempt to maintain blinding by not informing interviewers of the study hypothesis or the subjects' disease status. This is impractical in most studies, but given the use of controls who also have cancer and a high proportion of proxy interviews, effective blinding of interviewers *and* subjects may have been largely achieved here. Detailed data on smoke exposure at home as well as elsewhere, including pipe and cigar smoking, were collected. Pipe and cigar smoking are often not considered in ETS studies, thus constituting a potential source of exposure misclassification, and smoking at home

2501032158

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

should be a more meaningful index of smoke exposure than total smoking. What the authors termed "husband's smoking" actually includes smoking by related cohabitants as well. Presumably this was done both to increase subject numbers (by not excluding unmarried women) and to enhance detection of passive smoke exposure. However, it could cause some oversight with regard to classification of ETS exposure (e.g., a widow, living with a nonsmoking sister, whose husband had been a heavy smoker). Less understandable is the failure to include smoking by *un*related cohabitants and the inclusion of single women living alone. Diagnostic misclassification is unlikely given the histological verification of all cases *and* controls.

Both husband's at-home and total cohabitant smoking are associated with lung cancer, the association being stronger for at-home smoking. Both exposures show a statistically significant general increase in association with level of smoking, with substantial associations only at high levels. The adjusted association for at-home cohabitant smoking is much stronger (OR = 1.7; p = 0.03) than that for smoking outside the home (OR = 1.3; p = 0.13), a pattern consistent with home smoke exposure rather than some other smoking-related factor as the basis of the observed results. General ETS exposure, in contrast, was inconsistently related to lung cancer in the unadjusted analyses, with a stronger association for exposure within the last 5 years than within the last 25 (possibly attributable to better recall). No dose-response pattern is evident, however, and no association was found in the adjusted analyses.

The adjusted analyses include age, hospital, socioeconomic status, and year of diagnosis in a logistic regression model, along with the passive smoking variable. This adjustment did not significantly reduce the association between husband's smoking at home and lung cancer observed before the adjustment, but it did eliminate any association with general ETS exposure. Thus, the results for husband's smoking at home are probably not attributable to confounding by age, socioeconomic status, hospital, or temporal variables. Dietary factors, heating and cooking practices, and family history of cancer were not considered as potential confounders; thus, an effect by one or more of these factors cannot be ruled out.

The heavy reliance on proxy respondents and their uncertain impact on the analysis leaves some uncertainty to interpretation. On the favorable side of this issue, the authors' attempt to blind subjects and interviewers to the study hypothesis lessens the likelihood of potential bias from proxy response, and no effect due to respondent type was found in the adjusted analyses. Some of the exposure categories seem vague, but this would tend to reduce the magnitude of the observed association rather than to give rise to one. In summary, this study is suggestive of a dose-dependent association between smoking in the home and lung cancer, with reservations due to the use of proxies.

2501032159

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.11. GARF(Coh)

A.11.1. Author's Abstract

"Lung cancer mortality rates were computed for nonsmokers in the American Cancer Society's prospective study for three 4-year periods from 1960 to 1972 and in the Dorn study of veterans for three 5-year periods from 1954 to 1969. There was no evidence of any trend in these rates by 5-year age groups or for the total groups. No time trend was observed in nonsmokers for cancers of other selected sites except for a decrease in cancer of the uterus. Compared to nonsmoking women married to nonsmoking husbands, nonsmokers married to smoking husbands showed very little, if any, increased risk of lung cancer."

A.11.2. Study Description

This study examines the role of passive smoking in lung cancer among married women in the United States. It uses data collected in a large prospective study initiated by Cuyler Hammond of the American Cancer Society (ACS) in 1959. The ACS's objective was to evaluate the association between potential cancer risk factors and cancer mortality. Although data were collected on the smoking status of women and their spouses at the start of the study, Hammond thought the study data should not be used to estimate lung cancer death rates in relation to amount of passive smoking by female never-smokers. Specifically, Hammond notes that the study was not designed for that purpose, and no special information on the subject was obtained; information was available on the smoking habits of the husbands of many of the married women in the study, but not on the smoking habits of the former husbands of women who were widowed, divorced, separated, or married for a second time. More important is his statement that women in America at that time were not generally barred from public and social gatherings where men were smoking, and working husbands who smoked generally did much if not most of their smoking away from home (Hammond and Selikoff, 1981). Similar reservations are expressed by Garfinkel, who also notes that 13% of the women nonsmokers who died of lung cancer in the ACS study reported that they were previously married and that the classification of their exposure to their husbands' smoking may not be pertinent (Garfinkel, 1981, p. 1,065).

A total of 29 ACS divisions encompassing 25 states took part in the study; participating counties were in turn selected by division leaders based on feasibility. Data collection was undertaken by networks of volunteers set up within participating counties. Recruitment of subjects and subsequent follow-up monitoring were undertaken by volunteers who were instructed to enlist qualifying acquaintances. Subjects were restricted to persons more than 30 years of age whose household contained at least one person over 45 years of age. Illegal

250103216O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

immigrants and persons who were illiterate, institutionalized, or itinerant were excluded. Detailed questionnaires were distributed to subjects and all members of their household over 35 years of age. These questionnaires covered factors such as diet, alcohol consumption, and occupational exposures as well as smoking habits, but they did *not* address passive smoke exposure. Volunteers who recruited subjects were given responsibility for tracing the subject's vital statistics for the next 6 years and contacting living subjects again in 1961, 1963, and 1965 to complete a questionnaire on changes in smoking habits. Alternate researchers were appointed as necessary to replace volunteers who moved or quit. Finally, death certificates were obtained for subjects reported deceased; where death due to cancer was indicated, verification was sought from the certifying physician. Although follow-up initially ceased with 1965, in 1972 an additional follow-up was initiated in 26 of the original 29 ACS divisions and terminated in September 1972.

A.11.3. Comments

The passive smoking study being described (GARF[Coh]) was undertaken by assembling a subcohort of married women who reported that they had never smoked and whose husbands completed a questionnaire including smoking habits. This subcohort totaled 176,739 women out of the 375,000 never-smoking women enlisted by the ACS in 1959. Women were divided into three exposure categories based on their husband's smoking status—nonexposed for never-smokers, and low (high) for current smokers of less (more) than 20. Wives of former cigarette smokers and men who smoked cigars or pipes rather than cigarettes were excluded (Garfinkel, 1984); presumably these had already been excluded from the reported total (176,739). Mortality rates were computed by 5-year age intervals for unexposed women (i.e., wives of nonsmokers), from which the expected number of deaths for exposed women was estimated under the hypothesis that spousal smoking does not affect lung cancer mortality. The ratio of observed to expected deaths in the exposed group provides an age-standardized mortality ratio. This mortality ratio is 1.27 (95% C.I. = 0.85-1.89) for spousal smoking of under 20 cigarettes per day (low exposure) and 1.10 (0.77-1.61) for over 20 cigarettes per day (high exposure).

In a separate analysis, women healthy at the start of follow-up were divided into groups matched on age (5-year grouping), race, education, urban or rural residence, and occupational exposure of husband to dust, fumes, or vapors. Each of these matched groups was then subdivided into zero, low, and high exposure categories. The proportion of observed deaths in each category was multiplied by the proportion of subjects in the smallest category of the matched group relative to that category. This "adjusted" number of deaths was then summed across all groups with a given exposure and compared with the corresponding value for the unexposed (zero

2501032161

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

exposure) category to provide a mortality ratio. In addition, we conducted a Mantel-Haenszel analysis of mortality using data supplied by Garfinkel that yielded results similar to the author's analyses. Ages 35 to 39 and 70 to 79 were excluded due to insufficient numbers. After stratifying by age and correcting for time under study, the calculated lung cancer risk was greater in subjects whose husbands smoked, but the predicted risk at low exposure was greater than at high exposure. It is notable, however, that the lower risk at higher exposure is entirely attributable to the 50- to 59-year-old age group; otherwise, predicted mortality would be equivalent at the low and high exposure (see Table C-1 of this report).

The original ACS cohort study was a massive undertaking. By using it as the basis of his cohort, Garfinkel was able to assemble a very large number (over 170,000) of never-smoking married women. A cohort of this magnitude attains a number of lung cancer cases ordinarily feasible only by means of a large case-control study, while avoiding the attendant pitfalls of potential recall and interviewer bias associated with case-control studies. There are several important limitations, however, that make the results of this study difficult to interpret.

The ACS study was not designed to yield a representative sample of the general population. The sample of women is older (all at least 35 years of age, two-thirds between 40 and 59 at start of follow-up), more educated (only 5.6% were limited to a grade school education), and contains a much smaller proportion of ethnic minorities (only 6.8% nonwhite) than the general population (Stellman and Garfinkel, 1986). Although not representative of the population as a whole, the relative homogeneity of the subject population does reduce the potential for complications of interpretation that differences in ethnic or socioeconomic factors or both may pose, and it increases efficiency by not including subjects belonging to age groups unlikely to experience significant mortality during follow-up. Overall, the study population's unrepresentativeness strengthens rather than undermines the study's conclusions. It would have been useful, however, to confirm that exclusion of greatly underrepresented groups, such as nonwhites and persons with no formal education beyond the eighth grade, had no effect on the results.

Because the data on smoking habits were collected prospectively, no information on exposures prior to 1959 was obtained. Exposure history for the years before 1959 may be as important as for the 12 years of follow-up, however, if lung cancer has a long latency period, such as 20 years or so. Inclusion of persons whose exposure status may have changed markedly by 1959 could be a biasing influence. Neither were changes in exposure status during the follow-up period considered, despite the availability of data on smoking habits in 1961, 1963, 1965, and 1972. In fairness to the author, keep in mind that our comments are directed at evaluation of the

250103216

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

study for its contribution to the issues of passive smoking and lung cancer, although the ACS study was not designed to assess ETS exposure. The only data collected on ETS exposure are based on the spouse's *current* smoking habits at initiation of the study. If the ACS study had been directed at evaluation of health effects of ETS, these issues would likely have been taken into consideration to sharpen the classification of subjects with respect to ETS exposure. Overall, the likely consequence of these factors is to reduce the sensitivity of the study to detect an association between lung cancer and ETS exposure, but the potential for bias in the direction of a false positive cannot be ruled out. For example, if wives of smokers are more likely to become active smokers during follow-up than wives of nonsmokers, these changes in smoking status could bias results toward finding a positive association with passive smoking. (Relevant to this particular example, the authors state that "very few" subjects reported a change in their smoking status, but provide no further details. Also, 12 or fewer years is a short exposure to produce lung cancer. It is thus probable that any bias introduced by active smoking would be minor; furthermore, the fact that a stronger association was observed for low than for high levels of spousal smoking argues against a confounder associated with spousal smoking. Nevertheless, potential sources of bias may be present that influence the study outcome in either direction.)

During 1959-65, confirmation of primary lung cancer diagnosis was obtained from physicians for 78% of all cancer cases. Among 203 cases of lung cancer in nonsmoking women diagnosed by death certificate, confirmation attempts on an unspecified number of these cases found 34 misdiagnosed as primary lung cancer, whereas 10 primary lung cancers were discovered among cancers diagnosed as nonlung on death certificates. Thus, it appears that only about 85% of the death certificate diagnoses of primary lung cancer were accurate, while a small percentage of primaries were misdiagnosed as cancers of other cites. No confirmation of diagnoses was undertaken during the period after 1965 when nearly two-thirds (119 out of 182, according to data supplied to reviewers by Garfinkel) of the lung cancer deaths in the ETS study population were reported. In light of the misdiagnosis rates found for 1959-65, it is likely that a substantial percentage of the study's reported primary lung cancers in cases actually arose in other sites, whereas a substantial percentage of reported cancers of other sites actually arose in the lung. The resultant errors in subject classification probably bias the results toward no association (i.e., a false negative conclusion), *if* a positive association actually exists.

Loss of subjects to follow-up is another source of potential bias. A subsequent report on the ACS cohort (Garfinkel, 1985) states that, whereas more than 98% of the original cohort was successfully traced through 1965, over 10% (3 of 29) of the original ACS divisions declined to participate in the 1971-72 follow-up effort. In the study now under review, Garfinkel reports

2501032163

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

successful follow-up of 98.4% through 1965 and 92.8% through 1972, apparently not considering subjects in the division who declined to participate in the extended follow-up as losses. It thus appears that, whereas more than 98% of the original cohort was successfully followed up through 1965, less than 90% of the cohort was targeted for follow-up through 1972, and losses for this targeted group approached 7%. Such losses not only reduced the number of observed deaths—and, hence, the study's power—but introduced the possibility that differential loss to follow-up could have distorted the study's results. A greater proportion of losses among exposed subjects than among unexposed could partially mask a true positive association, whereas greater loss among the unexposed could potentially create a spurious association.

Aside from the issues above, the study controls for basic sources of potential confounding. Subjects were all of the same gender and marital status, and age was controlled for in all analyses. Analysis by groups matched on race, education, residence, and occupation, along with age, produced nearly identical results as the analyses standardized by age alone, indicating no confounding due to these and unlikely confounding due to other socioeconomic, occupational, or geographic factors.

In summary, this study predicts a weak positive association between spousal smoking at levels of 1 to 19 cigarettes per day and lung cancer, but only slight association at higher exposure levels; neither association is statistically significant. The lack of apparent dose-response pattern further undermines the association, but the confidence intervals of the point estimates for the high and low exposure groups overlap so broadly that the existence of a dose-response relationship cannot be ruled out entirely. Meaningful interpretation of the results for the issue of ETS exposure and lung cancer, however, is limited. As the study's objectives were directed elsewhere, the data collected on ETS exposure is limited to the status of spousal smoking at the start of the study. Past history and future changes in status are not well addressed. There is ample indication that death certificate diagnoses are not a reliable source for the selection and classification of subjects. Although a second 6-year follow-up period was undertaken to increase the follow-up period to 12 years, its success was limited by incomplete participation and, perhaps, by organizational difficulties related to long-term reliance on volunteers (who may relocate, change interests, lose contact with the subjects originally enlisted over an extended period, etc.). Even if the follow-up were entirely successful, however, 12 years of follow-up without regard to exposure experience is not a particularly long period to evaluate the lung cancer potential for ETS because the latency period associated with active smoking may be on the order of 20 years. Although the ACS study has been an important contribution to its main study objectives,

2501032164

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

the lack of information and potential sources of bias for the issue of passive smoking and lung cancer leave its assessment in question.

A.12. GENG

A.12.1. Author's Abstract

Not included in source.

A.12.2. Study Description

This study was conducted in Tianjin, where China's highest incidence of female lung cancer occurs, to illustrate the relationship between cigarette smoking and female lung cancer. The study explores both active and passive smoking, so the analyses for passive smoking apply to a subgroup of the larger subject population. The source of the study's subjects and the time over which they accrued is not specified. Subjects resided in Tianjin for over 10 years. The source of controls is not given, but they consist of females pair-matched with cases on race, age (± 2 years), marital status, and birthplace. It is unclear from the article whether cases were incident or prevalent and how controls were obtained. A draft summary description of this study (Liang and Geng, undated) from Liang indicates, however, that hospitalized cases (96) were matched with inpatient controls and general population cases (61) were matched with neighborhood controls.

The source of the study's exposure data is not clearly stated, but the draft from Liang indicates that all identified cases and controls were interviewed. No information on collection or verification of smoking or other data is provided. The authors state that cases and controls do not differ significantly in age, education, occupation, race, marital status, birthplace, or residence, but this refers only to the total study population of 157 cases and 157 controls that includes active smokers; the same similarity may not hold for the 54 cases and 93 controls used in the passive smoking analysis. Tumor types are provided for 85% of the total case population, but not specifically for the passive smoking subpopulation; adenocarcinomas (36.9%) predominate, being about twice as common as squamous (22.3%) or small cell (19.7%) tumors. Although nearly 85% of the total cases were diagnosed histologically or cytologically, it does not appear that verification of diagnosis or primary status of tumor was undertaken by the authors, and no information on tumor distribution is supplied.

A nonsmoker (which usually means never-smoker) is ETS exposed if the spouse smokes. Presumably women not currently married are excluded from the analysis, although they could have been included with some assumption made regarding their exposure status. Information on dose and duration of exposure was collected but not used in the passive smoking analysis, and it is

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

not indicated if cigar or pipe smoke was included. ETS exposure from parents and colleagues is reported to have been evaluated. The parental smoking referred to is apparently in adulthood, as cohabitants in the home, but that is not made explicit. Exposure during childhood was not specifically addressed.

Among the ETS subjects, 34 out of 54 cases and 41 out of 93 controls were exposed. This yields a statistically significant crude odds ratio of 2.16 (95% C.I. = 1.03-4.53) for husband's smoking. No analyses adjusted for age or other factors are reported. On a rather confusing note, an odds ratio of 1.86 is cited twice later, but that value is inconsistent with the odds ratio of 2.16 from the raw data. Whether this is an error or the product of an unspecified adjustment by conditional logistic regression, which the authors employ for other purposes throughout the paper, is unknown. The odds ratio increases with the number of cigarettes smoked per day by the husband and with the duration of the husband's smoking. The odds ratios for smoking rates of 1 to 9, 10 to 19, and 20 or more cigarettes per day are 1.4, 2.0, and 2.8, respectively. For 1 to 29, 20 to 39, and 40 or more years of exposure, the odds ratios are 1.5, 2.2, and 3.3, respectively. No tests for trend are cited, and the relevant data are not given. Consideration of ETS exposure from smoking by father, mother, or "colleagues" reportedly yielded no results that are "quite significant." No further details are provided, and it is not clear whether these results consider past smoking status or apply only to current status.

The authors conclude that active and passive smoking are the most important risk factors for female lung cancer in Tianjin. They attribute 35% to 42% of lung cancer occurring in their nonsmoking female population to passive smoking. Female lung cancer is also found to be associated with other factors, such as occupational exposure, with an odds ratio of 3.1 (95% C.I. = 1.58-6.02); history of lung disease, with an odds ratio of 2.12 (95% C.I. = 1.23-3.63); and cooking with coal, where the odds ratio increases with the duration of exposure from 1.5 to 5.5 (see Table 8 of this reference).

A.12.3. Comments

The quality of this study is difficult to assess given the dearth of details supplied by the authors. Certainly the number of nonsmoking cases and controls included is more substantial than in some other studies, and the reported association between passive smoking and lung cancer is statistically significant. Questions regarding the mechanics of data collection and analysis, however, remain unanswered.

Exposure and other data were obtained from hospitalized subjects at bedside and from others in their homes. The extent (if any) to which information was obtained from proxy

250103216

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

responses, or interviews were denied, is unspecified. No blinding was employed, but that may have not been feasible. Despite the reported similarity of the demographic characteristics of the total case and control populations, dissimilarity cannot be ruled out within the subgroup used for ETS analyses. Although the whole study, including active smokers, is matched on several variables, the matching need not apply to the ETS subjects alone.

Lack of validation of diagnostic and exposure information may have led to substantial misclassification, although the fact that 85% of the lung cancer diagnoses were obtained via histology or cytology suggests that diagnostic misclassification would not have been extreme. Lack of consideration of former smoking status is a potential problem. Inclusion of former smokers among the nonsmokers, in combination with a tendency for former smokers to marry smokers, could produce an upward bias in the odds ratios.

Finally, although the crude odds ratio of 2.16 for passive smoking is statistically significant, it does not take into account even the most basic potential confounder—age. For the larger case-control population (including smokers), occupational exposure (OR = 3.1), history of lung disease (OR = 2.64), and cooking with coal (OR = 1.54-5.56, rising with cumulative exposure) are statistically significant risk factors that the authors claim have joint effects with smoking, yet the ETS analysis is not adjusted for these likely confounders. The anomalous odds ratio of 1.86 given later in the results *may* have been adjusted for age or other factors, but there is no way to tell.

In summary, the study's results are consistent with the hypothesis that passive smoking increases the risk of lung cancer, but they are not definitive. More detail regarding the mechanics of the study is needed to assess its general validity. If warranted, a clearer and more complete analysis of the study's data regarding passive smoking, including consideration of the information on dose, duration, and potential confounders already available, would then be useful. For the current evaluation of epidemiologic evidence on ETS exposure and lung cancer, too many questions remain about the design and execution of the study to properly interpret the data and assess the authors' conclusions.

A.13. HIRA(Coh)

(*Note:* Because of the many publications relating to this study, a different format of presentation is used.)

This cohort study and a later case-control study based on it were undertaken to explore the relationship of passive smoking and other factors with lung cancer in Japanese women. Subjects

250103216?

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

and data used in this study were, however, drawn from a larger study that was not designed to investigate passive smoking.

An exploratory study of mortality determinants targeting adults at least 40 years of age inhabitating 29 health center districts in Japan was initiated in 1965. In autumn of 1965, more than 90% of the target population was interviewed to ascertain the status of lifestyle factors that might affect health (e.g., cigarette smoking, alcohol consumption, and occupation). Individuals, including husbands and wives, were interviewed separately. Follow-up of the interviewees was conducted using a combination of an annual census of residents and death certificates to monitor mortality. Mortality, as determined by death certificate, was the outcome variable. Hirayama used this study population to examine the potential effect of passive smoking on lung cancer mortality. In 1981, he reported the results derived from the first 14 years of follow-up (through 1979) in the *British Medical Journal*.

A total of 142,857 women were interviewed in 1965, of whom 91,540 were nonsmokers whose husbands had also been interviewed regarding smoking status. Using their husbands' smoking status as a surrogate for exposure to ETS, Hirayama calculated lung cancer mortality rates for comparison of women married to smokers with women married to nonsmokers; rates were also calculated using various strata of spousal smoking intensity (number of cig./day), as well as age and occupation. A total of 346 lung cancer deaths occurred in this cohort during the first 14 years of follow-up.

After standardization for age and occupation, it was found that women whose husbands smoked daily had a higher annual rate of lung cancer mortality than did women whose husbands were nonsmokers or only "occasional" smokers. The rate increased with the level of smoking (e.g., 8.7/100,000 annually for no or occasional smoking, 14.0 for smoking 1-19 cig./day, and 18.1 for 20+ cig./day). Higher rates and a dose-response pattern were observed in women married to smokers after stratification on either husband's age or agricultural work status. Mortality due to two diseases associated with active smoking, emphysema and asthma, was also higher in wives of smokers and increased with exposure. Conversely, mortality due to two cancers not linked to active smoking, cervical and stomach cancer, was no higher in wives of smokers. Consideration of husbands' drinking habits had no significant impact on mortality for lung cancer or other diseases mentioned above.

Further study results appeared in the October 3, 1981, issue of *British Medical Journal*. Among other things, results were presented by husband's age in 10- instead of 20-year intervals and for 10 occupational categories instead of 2. These tabulations revealed a statistically significant overall association between husbands' smoking and lung cancer mortality with a dose-

250103216B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

response pattern (1.00 RR for nonsmokers plus former smokers, 1.44 RR for medium smokers, and 1.85 RR for heavy smokers). Also of interest was a breakdown of lung cancer mortality and smoking habits in greater detail for both husband and wife. Notably, nonsmoking *husbands* with smoking wives showed a higher lung cancer mortality rate (RR = 2.94) than did those with nonsmoking wives. Because nonsmoking husbands with smoking wives were rather rare, however, the numbers in this stratum were low (only seven deaths); thus, the observed association was not statistically significant.

In 1984, Hirayama published results of an additional 2 years of follow-up of his cohort in *Preventive Medicine*. The same basic associations reported after 14 years of follow-up for spousal smoking and lung cancer remained after 2 additional years of follow-up. Mortality rates increased with increasing exposure after stratification by age of husband, occupation, geographical area, and time period during study; a trend had been reported after stratification for age of wife at start of study only for ages 40 to 49 and 50 to 59. It was also reported that the elevation of lung cancer mortality in nonsmoking women married to smokers was significantly less among women who consumed green-yellow vegetables daily (e.g., for spousal smoking of 20+ cig./day, the RRs for disease mortality were 1.63 and 2.38). No such pattern was observed for ischemic heart disease. In addition, a statistically significant excess of para nasal sinus cancer in nonsmoking wives of smokers had been observed, which showed an apparent dose-response relationship across four smoking categories, culminating in an RR of 3.44 for spouses of smokers of more than 20 cigarettes per day. That effect dwarfed those related to social class and dietary factors that were also examined.

In 1988 Hirayama reported the results of a case-control study nested within his cohort in *Environmental Technology Letters*. To explore the relationship of women's age at marriage, as well as husbands' smoking status with lung cancer mortality, lung cancer cases occurring among nonsmoking women in the cohort study were contrasted with stomach cancer cases as controls. Including only women under 59 years of age at the start of the cohort, the study divided husbands' smoking into three categories—none, 1 to 19, and 20 or more cigarettes per day. Age at marriage was also trifurcated in 19 or fewer, 20 to 23, and 24 or more years. Apparently as a result of exclusion of women over the age limit or because of missing data, only 115 cases and 423 controls were ultimately compared out of the 200 lung cancers and 854 stomach cancers among the nonsmoking female cohort. Adjusting for woman's age and husband's smoking category resulted in odds ratios for lung cancer of 4.95, 1.76, and 1.41 for the respective age-at-marriage groups; the first two of these odds ratios were statistically significant. An additional comparison found

2501032169

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

that among lung cancer cases, the mean age at first marriage to a smoking husband was nearly 8 years less than the mean age at start of smoking for active smokers.

A greatly expanded nested study was presented in the following year (Hirayama, 1989). The study was designed to explore the potential for confounding of the relationship between lung cancer and spousal smoking by dietary habits. A "baseline" sample of 2,000 nonsmoking wives with known spousal smoking habits, aged 40 to 69 at the start of the cohort study, was randomly selected from the available cohort of 90,458 for comparison with the 194 lung cancer cases occurring in equivalent subjects within the cohort. After determining that the age distributions of the case and baseline groups were very similar within smoking categories, the combined population was stratified on daily versus less-than-daily consumption for each of five food types (green-yellow vegetables, fish, meat, milk, and soybean paste soup) and wives with smoking and nonsmoking husbands were contrasted to assess differences in dietary habits. After adjustment for wife's age and husband's occupation, only daily meat consumption was significantly more common among wives of smoking husbands, and this was limited to smokers of 20 or more cigarettes per day. Calculation of odds ratios for dietary habits resulted in a "significant" elevation only in daily fish consumers (OR = 1.365, 90% C.I. = 1.05-1.77; Table IV). A nearly significant *lowering* of the odds ratio was found in daily meat consumers.

Finally, odds ratios were calculated for lung cancer adjusted by wife's age, husband's occupation, and each of the dietary habit categories in succession. A dose-response pattern was observed between lung cancer and husband's smoking that persisted after adjustment for any of the five dietary factors. Odds ratios for the five dietary habit categories ranged from 1.42 to 1.69 for former smokers and smokers of 1 to 19 cigarettes per day, and from 1.66 to 1.91 for smokers of 20 or more cigarettes per day compared with nonsmoking husbands. The observed trend was highly statistically significant, regardless of which factor was adjusted for in the calculation.

A.13.1. Chronology of Controversy

Publication of Hirayama's initial 14-year follow-up results in 1981 provoked a sizeable volume of commentary in the scientific literature. Following the release of updated results in 1983-84, the study attracted little controversy until the latter part of the 1980's, when criticisms were directed at the study by a number of authors. This process reached its culmination in response to the EPA's release for external review of the document *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children*, which placed considerable emphasis on Hirayama's results. An author-by-author, letter-by-letter consideration of the arguments regarding Hirayama's work would be dauntingly duplicative and

250103217

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

tedious. Instead, the most-discussed concerns will be highlighted, followed by an overall assessment of the study as it stands today.

Chronology of Selected Events Relevant to the Hirayama Cohort Study

Jan. 7, 1981	Results of cohort study are published in *British Medical Journal* (282:183-185).
Oct. 3, 1981	Comments and letters to the editor by Kornegay and Kastenbaum (of the U.S. Tobacco Institute), Mantel, Harris, and DuMouchel, and MacDonald appear re: Jan. 7 article in *British Medical Journal*, along with the author's reply.
March 3-5 & July 10-15, 1983	Hirayama presents updated results for his study cohort incorporating an additional 2 years of follow-up (for a total of 16 years) to the International Lung Cancer Update Conference in New Orleans and the 5th World Conference on Smoking and Health in Winnipeg, Canada.
Dec. 17, 1983	Updated results of the cohort study are published in *Lancet*.
1984	Results presented in conference of July 1983, and in summary form in *Lancet* later that year, are published in full in *Preventive Medicine*. In addition, Hirayama now reports a statistically significant increase in brain tumors with husbands' smoking. In a round-table discussion published in the same journal, Lee proposes that misclassification of active smoking status may have biased Hirayama's results.
1985	Another publication of results for the 16-year follow-up appears in *Tokai Journal of Experimental Clinical Medicine*.
1987	Hirayama includes previously published study data in a book chapter (Aoki et al., 1987).
1988	Uberla and Ahlborn publish an article from the *Proceedings of the Indoor Ambient Air Quality Conference* in London (which is essentially the same as an earlier presentation at the 1987 Tokyo International Conference on Indoor Air Quality) criticizing the Hirayama study on several grounds. Their primary assertion is that correction for the cohort's age distribution removes the apparent effect of spousal smoking.
1988	Hirayama publishes the results of nested case-control study based on cohort study data in *Environmental Toxicology Letters*. Estimated risk of lung cancer is reported to increase with earlier age of marriage to smoker.
1989	Layard and Viren publish a paper presented at the Conference on the Present and Future of Indoor Air Quality in Belgium. Making their own projections of expected deaths and estimating losses to follow-up, they conclude that mortality rates were anomalously low and follow-up losses unacceptably high in the Hirayama study.

2501032171

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

1989 Hirayama publishes nested case-control results in *Present and Future of Indoor Air Quality*. Positive association of husband's smoking and lung cancer with dose-response pattern reported after adjustment for dietary variables.

A.13.2. Some Major Critical Works

A basic point raised by MacDonald (1981) and others soon after publication of Hirayama's initial results concerns the selection of the study's sample population. It appears that the 29 health centers included in the study were selected on grounds of convenience rather than to provide a randomly sampled, representative cross-section of the Japanese population. The resultant sample may thus be unrepresentative of the Japanese population as a whole.

A convenience sample may still produce a fairly good cross-section of the population, and Hirayama replied in 1981 that "the satisfactory representativeness [of the study population] . . . with regard to demographic and social indices was confirmed after the survey." He did not, however, provide supporting data. MacDonald (1981) contends that the six prefectures from which the sample was drawn are relatively industry-heavy (which does not necessarily contradict Hirayama's contention); data presented by Hirayama (1983) showed that 40,390 of the cohort's wives were married to agricultural workers, 19,264 to industry workers, and 31,886 to "others," which would indicate some overrepresentation of agricultural areas. Women aged 70 or more are clearly underrepresented, composing less than 1% of the study's 40-and-older nonsmoking female population. Thus, the cohort may be unrepresentative to some degree, but *how* unrepresentative is unclear.

The key problem arising from an unrepresentative sample is that it may limit generalizability of results derived from that sample to the population as a whole. In lieu of good reasons to think that the association between exposure and disease would be different in the study population and the general population, however, the possibility of an unrepresentative sample assumes less importance. And, as will be seen in the subsequent discussion of possible confounders, similar patterns of association were observed in a number of demographic subgroups.

Misclassification may occur in any epidemiologic study. Most of the critical commentary has focused on potential misclassification of exposure status. Because the study relies on interview data to establish smoking status, misreporting by interviewees may affect accurate classification of both wives *and* their husbands' smoking habits. It has been argued that women are especially likely to misrepresent their smoking habits because smoking is considered less socially acceptable for women than for men, particularly in Asian societies. Such misclassification

250103217

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

would tend to reduce the degree of association between passive smoke exposure and its effect(s) if women in the "exposed" and "unexposed" groups were equally likely to misreport their own smoking. One of the most prominent criticisms leveled at the Hirayama study postulates a differential misclassification of smoking status in women. Peter Lee (Lehnert, 1984) raised the argument that if women married to smokers are more likely to be (or to have been) smokers than are women married to nonsmokers, and a given percentage of smoking women claim to be nonsmokers, then purportedly nonsmoking wives of spousal smokers will include a higher proportion of active smokers than wives of spousal nonsmokers. This will cause bias in the direction of a positive association. Arguments over the probable size of this bias have occurred with estimated elevations in risk ranging from a few percent to around 50%, depending on assumptions regarding the extent of misreporting, the risk inherent in active smoking, and the degree of marital concordance between smokers (Lehnert, 1984; Wald et al., 1986; Lee, 1987a and b).

Uberla and Ahlborn (1987) raised a number of points regarding the Hirayama study, including those previously mentioned. Citing the "severe selection bias by age," the authors report that the increase in risk with spousal smoking disappears when this bias is corrected for. The study population in fact contained a very small proportion of women aged 70 or more (only about 1%)—so small that the rates generated by nonsmoking married women aged 70 or more are too unstable to provide meaningful results. But by taking the negative results observed in this tiny, unstable stratum of the cohort and weighting them to "correct" for the underrepresentation of this age group, the overall association is made to disappear. Such a "correction" is meaningless. In addition, Hirayama (1990) has noted that the authors inappropriately adjusted to the total female population rather than to the population of currently married females, and characterized the adjustment as "neither of scientific significance nor of creative value."

The authors also essentially take Lee's approach to the differential misclassification problem and claim that a modest differential misclassification "leads to risk ratios of around unity." As seen previously, this argument is plausible but purely speculative—and, of course, potential biases toward the null are ignored in this and other "corrections." The authors conclude that "the null hypothesis . . . is consistent with the Hirayama data in the same way as the alternative." But unless one applies the aforesaid "corrections," the Hirayama data is, in fact, *more* consistent with the hypothesis of association than with the null hypothesis.

Layard and Viren (1989) estimated "projected" mortality rates for a cohort with the age and time distribution found in the Hirayama cohort by applying "standard demographic life table procedures" to year and age-specific life table data from United Nations and Japanese sources.

2501032173

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

They concluded that female all-cause and lung cancer reported rates were only 76% and 85%, respectively, of projected values. In a separate analysis, the authors also "calculated the numbers of person-years that would have been observed in the cohort if there had been 100% follow-up" from the reported numbers of deaths. The assumptions used in this calculation are unstated. The authors then estimated, based on the difference between their person-years for 100% follow-up and the reported person-years, and an assumption that 8 years of observation were lost on average for each person lost to follow-up over the 16-year course of the study, that approximately 10% of the cohort was lost to follow-up. Dismissing other possible causes of their estimated mortality deficits, Layard and Viren conclude that "it is possible that biases exist in the data which might invalidate an observed relationship between exposure to ETS and mortality."

Of course, acceptance of Layard and Viren's conclusions must start with acceptance of the validity of their assumptions and calculations, not all of which are stated explicitly. Beyond that, their rejection of alternative explanations for the difference between projected and reported deaths is not convincing. For example, random sampling variation and regional variations in death rates are both dismissed because neither could produce an effect as large as that observed, although the authors' figures indicate that in combination they could well account for a sizeable portion of the difference. Likewise the effect of admitting only (initially) "healthy" people to the cohort is dismissed based on the observation of "still very substantial cohort deficits in the last years of the study" without specification of how substantial such deficits were and ignoring the fact that a pattern in which all-cause mortality is most affected and cancer mortality least, as their calculations showed, is the expected pattern for an effect of selection of healthy individuals. Finally, to produce a spurious association, a bias must operate differently on the exposed (smoking spouse) and unexposed (nonsmoking spouse) groups, and no evidence is provided that supports such a pattern. Lacking such a pattern, the most likely effect of loss to follow-up is a reduction in the observed associations due to missing mortality events. The effect of selecting an abnormally healthy cohort would in a strict sense limit generalizability of conclusions but would not in itself produce an exposure-effect association when none actually existed.

A.13.3. Critique and Assessment

Hirayama's cohort is drawn from a study population assembled to explore the associations between a number of potential health-influencing factors determined via interview and subsequent mortality. Thus, the study was not designed to investigate passive smoking and lung cancer specifically. Most of the weaknesses attributable to Hirayama's study derive from this fact.

05/15/92
2501032174

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The only indicator of ETS available to Hirayama was self-reported smoking status at time of baseline interview. Thus, misclassification of spousal smoking status is possible and change in status over time, modifiers of exposure to spousal smoking, and other sources of ETS exposure cannot be determined.

As previously seen, an overrepresentation of current and former active smokers claiming to be nonsmokers among wives of tobacco smokers probably biases the association between spousal smoking and lung cancer in reported nonsmokers upward. Even the leading proponent of this argument, however, states that unless this bias is much stronger than it appears to be in U.S. and Western populations, it could not account for the major part of the observed results (Lee, 1990). Lack of information regarding amount of smoking actually done in the home and in the presence of the spouse, room size and ventilation, and other exposure modifying factors must lead to imprecision in the estimates of exposure via spousal smoking. This imprecision would make an actual ETS-lung cancer association more difficult to detect. The fact that spousal smoking exposure, even if precisely measured, is an imperfect surrogate for total ETS exposure because workplace and ambient environmental sources are not assessed introduces a similar effect. Both of these problems would thus introduce a bias toward the null, suggesting that the study's results are an underestimate of the real association.

Mortality information was derived from death certificate linkage. It has been contended that lung cancer is routinely overdiagnosed as a cause of death on death certificates, thus undermining the study's credibility. But the resultant misclassification of cause of death would presumably be nondifferential and thus bias results toward the null. To cause overestimation of the association, a greater proportion of women in the spousal smoking groups than in the nonsmoking group would have to be falsely diagnosed as having lung cancer. Because the study cohort was made up of *nonsmoking* women, there would be little reason for such a pattern. (Unless, of course, all such cases came from women who falsely reported their initial smoking status or took up smoking in the course of the study *and* the misclassification/smoking habit concordance hypothesized by Lee were actually strongly at work.)

No information is given regarding whether the same interviewers interviewed both husbands and their wives. Thus, interviewers may not have been blind to spousal smoking characteristics of interviewees. This is likely to have been of little importance, however, because the outcome—lung cancer mortality—was measured prospectively, and thus did not occur for some time *after* exposure had been assessed. If information bias was to some extent operant in the interview, the most likely scenario would find women whose husbands smoked being probed more strongly for admission of their own smoking than were women whose husbands did not smoke.

2501032175

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

This would tend to *reduce* underreporting of active smoking in the "exposed" group relative to the "unexposed" group. The result would be to *lower* the observed association between husbands' smoking and lung cancer mortality.

Hirayama's cohort includes only married, reportedly nonsmoking women who were at least 40 years of age and "healthy" at the start of the study. In addition, almost all of these women were under 70 years of age, and agricultural families composed a relatively large part of the cohort. Thus, the cohort does not present a representative cross-section of the Japanese population as a whole. Nevertheless, there is little obvious reason why a relationship between spousal smoking and lung cancer mortality found in this cohort should be dismissed on the grounds that it is not generalizable to the greater Japanese (or other) population. In fact, one could argue that by studying a more homogeneous population in the cohort, the possibilities for bias due to differences between exposed and unexposed groups are reduced.

The possibility that confounding by other risk factors brought about an observed association must be considered in any study. For lung cancer, of course, smoking, gender, and age are major risk determinants. Restriction of comparison groups to same-gender nonsmokers avoids potential confounding by gender or smoking (but see misclassification discussion regarding smoking status). Age is only partially restricted in the study design, so its consideration in the analysis is essential. Hirayama chose to control for husband's age in analyzing the cohort study's results. All observed associations persisted after such adjustment. Spousal ages *should* be closely correlated, but direct adjustment using the subject's own age rather than the age of their spouse would clearly be preferable. One such analysis *was* supplied (Hirayama, 1983b), and in it a significant association between spousal smoking and lung cancer mortality persisted. Furthermore, in analyzing the nested case-control studies, adjustment for wife's age was used throughout, which produced findings that confirmed the results of the cohort study.

The potential role of confounding by other factors in the observed results has received considerable emphasis. A correlation between smoking and lower socioeconomic status with concomitant lifestyle and environmental differences could be expected. Among these differences, particular attention has been paid to the possible effect of dietary factors, particularly low beta carotene intake, and occupational exposures, both of which, some hold, should correlate with spousal smoking and thus could bring about the observed association even if spousal smoking and ETS exposure has no effect. Yet, neither stratification on daily green-yellow vegetable consumption—the best available surrogate for beta carotene intake in the data—nor on agricultural versus nonagricultural occupation of husband eliminated the association between spousal smoking and lung cancer mortality in the cohort study. Similarly, adjustment for husband's occupation and

2501032176

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

any of five dietary habit characteristics, along with wife's age, yielded similar results in the case-control approach. Thus, neither of the major proposed confounders satisfactorily accounts for the observed results.

Because the data set does not contain the necessary information to examine confounding due to differences in cooking practices (such as stir-frying), this cannot be ruled out, although such practices might be expected to covary with some of the dietary factors considered in the analyses. Similarly, use of coal for cooking or heating cannot be directly assessed, though a degree of covariance with dietary habits or occupation is likely.

Husband's drinking habits were only marginally associated with lung cancer risk; mortality rates stratified by both drinking and smoking would have been more useful (and stratification by wives own drinking habits would have been more useful still).

When lung cancer mortality among wives is stratified by wife's age (in 10-year increments) and husband's smoking category, a clear dose-response pattern is seen only in the 40 to 49 and 50 to 59 age strata, whereas a decrease in mortality with spousal smoking is seen in the 70 and older stratum. Given that the latter stratum includes less than 1% of the cohort and very few deaths, its rates are too unstable to have much confidence in. The dose-response pattern does become weaker with ascending age strata, however, which has led to conclusions of inconsistency with an ETS-lung cancer connection and presence of confounding. Hirayama has proposed that age-related increases in spousal mortality, smoking cessation, and decreased time spent in husband's proximity during the follow-up period may account for the observed pattern (Hirayama, 1990). The proximity effect seems questionable, because retirement of older husbands would eliminate time spent away from the house at work, but the other arguments are plausible. Alternatively, older women recently married to smokers may be more likely to die from competing causes of death that increase with age before passive-smoke cancer develops. Remarriage, possibly to a spouse whose smoking habits differ from those of the former spouse, would also increase with age and could lead to misclassification of (former) exposure with a bias toward the null. (It is unfortunate that history of former spouses' smoking habits and recency of marriage were apparently not obtained in the baseline interview or the aforementioned problems could be readily addressed.) Temporal trends in some risk modifiers, such as dietary factors, could also play a role.

Confounding cannot entirely be ruled out in certain instances. But the underlying question that must be raised in this regard is the following: *If* the spousal smoking group contains a disproportionate number of individuals with risk-elevating factors such as poor diet, lack of exercise, low socioeconomic status, and occupational hazard exposure, and these factors are

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

sufficient to produce an increase in lung cancer mortality relative to the spousal nonsmoking group, despite an absence of any real smoking effect, *why* does this multitude of risk factors result in elevations of established smoking-related diseases only and no substantial elevation of risk of other causes of mortality (except brain cancer, which encompasses relatively few deaths)?

In considering the study's results in broader terms, Hirayama's findings are consistent with the hypothesis that exposure of nonsmoking women to passive smoke via spousal smoking increases risk of lung cancer. The observed association is statistically significant. And the persistence of the association after stratification on numerous variables, the observation of a parallel association in nonsmoking husbands of smoking wives, the appearance of associations with other smoking-related diseases, the existence of a dose-response pattern in most analyses of strata containing adequate numbers, and the production of similar conclusions by either cohort or case-control approaches argues against attribution of results purely to chance or confounding.

Possible inclusion of active smokers among "nonsmoking" spouses of smokers through misclassification bias or differential change in smoking status during follow-up remains the study's greatest weakness. This problem could have been addressed by follow-up interviews or questionnaires coupled with verification of smoking status by alternative means in a subsample of the cohort, and still could be. In addition, losses to follow-up and failure to use more sophisticated survival analysis techniques are weaknesses that probably reduced the study's power.

Overall, the Hirayama study provides supportive, although not definitive, evidence that ETS exposure increases lung cancer risk.

A.14. HOLE (Coh)

This prospective cohort study was undertaken in the towns of Paisley and Renfrew, Scotland. The primary objective was to explore the relationship between passive smoking and cardiorespiratory symptoms and mortality, including lung cancer. The towns were selected because they are situated in an area with a high incidence of lung cancer. All persons residing in these towns between 45 and 64 years of age, inclusive, were visited between 1972 and 1976. Each was asked to complete a self-administered questionnaire and to visit a cardiorespiratory screening center where further interviews were conducted; 80% (15,399 persons) responded.

Participating households in which at least two "apparently healthy" subjects lived were included in the study, yielding a study population of 3,960 males and 4,037 females. Data on smoking habits were obtained from the questionnaire and verified by interview at the screening visit. Mortality among subjects was traced using the Scottish National Health Service Central Register and General Register offices (for death certificate linkage), as well as the national cancer

250103178

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

registry system. Results for follow-up through 1982 were published in 1984 (Gillis et al., 1984). The primary results reported here are for follow-up through 1985, published in 1989 (Hole et al.). In addition, the results of unpublished data extending follow-up through December of 1988 are reported (personal communication from Hole to A.J. Wells).

Smoking habits were divided into three categories: persons who have never smoked, former smokers, and current smokers. In addition, the number of cigarettes smoked per day was obtained for current smokers. Both pipe and cigar smokers were excluded from the group who had never smoked. Never-smokers with former or current smokers as cohabitants in their household were classified as passive smokers; otherwise never-smokers were classified as "controls." This classification yielded 1,538 passive smokers and 917 controls for both sexes combined. The corresponding numbers for females alone are 1,295 and 489.

The number of lung cancer deaths among females occurring in the cohort during the follow-up period is only six, too small to be of statistical consequence. The unpublished data extending follow-up through 1988 includes one additional female lung cancer death that occurred subsequent to 1985. The crude relative risk is 2.27 (95% C.I. = 0.40-12.7), which is in the direction of a positive association between ETS exposure and lung cancer. The extremely wide confidence interval is the result of the small number of cancer deaths being compared and indicates that the data could easily arise when the true value of the relative risk is almost any value. After adjustment for age and social class, the relative risk is 1.99 (95% C.I. = 0.24-16.72). Lung cancer incidence was somewhat higher than mortality (10 cases vs. 7 deaths), yielding an adjusted relative risk of 1.39 (95% C.I. = 0.29-6.61). The relative risks for adjusted mortality (5.30) and incidence (3.54) were higher in males than in females but were based on even fewer cases (four deaths, six incident cases).

Although the observed association could easily occur by chance, it is a useful contribution to the pool of evidence on lung cancer and passive smoking. Consequently, it is worth noting that the observed associations are not likely to be attributable to confounding by other factors, because they persisted after control not only for age and gender, but for social class, diastolic blood pressure, serum cholesterol, and body mass index. Thus, differences in lifestyle or environmental factors such as diet, housing, and employment between passive-smoking households and nonsmoking households is an unlikely source of the results. Specific adjustment for potential occupational exposures or radon were not carried out, but these variables would presumably covary with social class to a great extent.

As for other sources of bias, interviewer bias can be discounted because subjects were "apparently healthy" at interview and supplied smoking information before cardiovascular

2501032179

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

screening, and the investigators did not begin determining the passive smoking status of subjects until 1983 (for the first published study on this cohort). The extent of loss to follow-up is not specified, so one cannot tell whether this was a potential source of problems. However, linkage was carried out through two registries for general mortality and an additional registry specifically designed for cancers. Diagnoses of cancer mortality from death certificates were checked against cancer registry records for verification, thus reducing potential inaccuracies attendant on use of death certificates.

Some data regarding misclassification were collected in an additional questionnaire administered to a portion of the cohort at some unspecified point in the study. Among controls, 5% said that their household contained a smoker—presumably someone who had not met the inclusion criteria (e.g., age 45-64) for the study. Thus, a small portion of the control group was actually currently exposed, which would produce a slight bias toward the null. Differential misclassification of smokers as never-smokers resulting from concordance of smoking habits among cohabitants cannot be assessed or ruled out, despite the authors' suggestion that persons cohabitating with smokers may be more likely to falsely claim to be smokers themselves, providing a bias toward the null.

In summary, this study appears well-designed and executed, but the number of ETS exposed subjects is small. Although its influence may be relatively small, there are no apparent methodological problems that would limit its usefulness otherwise.

A.15. HUMB

A.15.1. Author's Abstract

"As part of a population-based case-control study of lung cancer in New Mexico, we have collected data on spouses' tobacco smoking habits and on-the-job exposure to asbestos. The present analyses include 609 cases and 781 controls with known passive and personal smoking status, of whom 28 were lifelong nonsmokers with lung cancer. While no effect of spouse cigarette smoking was found among current or former smokers, never smokers married to smokers had about a two-fold increased risk of lung cancer. Lung cancer risk in never smokers also increased with duration of exposure to a smoking spouse, but not with increasing number of cigarettes smoked per day by the spouse. Our findings are consistent with previous reports of elevated risk for lung cancer among never smokers living with a spouse who smokes cigarettes."

2501032180

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.15.2. Study Description

This population-based case-control study was conducted through the New Mexico Tumor Registry during 1980-84. The original purpose was to explain differing lung cancer occurrence in Hispanic and non-Hispanic whites in New Mexico. The study questionnaire included questions on spousal smoking and on indirect exposure to asbestos through a spouse's job. The current report describes the risks associated with those exposures in smokers and nonsmokers. The data on ETS exposure in nonsmokers is extracted from the larger study containing smokers.

For the whole study, a total of 724 eligible primary lung cancer patients were identified, of which 641 were interviewed (89%). About half (48%) of the case interviews were conducted with the subject. Information on the remaining subjects was obtained from surrogates, generally the surviving spouse or a child. Cases were collected in two series, the first consisting of patients with cancer incident in 1980-82. That group includes all cases less than 50 years of age and all Hispanics, but not those exclusively. The number of cases was supplemented by a second series of patients with cancer incident to a 1-year period beginning November 1983. Most of the controls were selected by random telephone sampling, but some older subjects were randomly selected from Medicare participants. The control group was frequency-matched to the cases for sex, ethnicity, and 10-year age category, at a ratio of approximately 1.2 controls per case. Interviews were held for 784 of the 944 eligible controls, with 98% of the responses from subjects.

The term "never-smoker" means not a cigarette smoker, where the latter is defined to be someone who has smoked at least 6 months. The smoker classification is divided further into current smokers and ex-smokers. The current smoker status includes smokers who have stopped within 18 months prior to the interview; the ex-smoker status applies if smoking ceased more than 18 months prior to interview. Assuming that the minimum 6-month duration of smoking is intended to apply to current and ex-smokers, never-smokers could have smoked previously for up to 6 months.

An ETS-exposed subject is one ever-married to a spouse who smoked cigarettes, regardless of the spouse's use of pipes or cigars. No information was obtained on exposure to ETS from other sources, such as from other household smokers, in the workplace, or from parental smoking during childhood. Measures of ETS exposure from spousal smoking include duration of exposure (in years) and the average number of cigarettes smoked per day by the spouse. The ETS subjects (never-smokers) include 20 (4) female (male) cases and 162 (130) controls (the article reports eight male cases, the number used in much of the analyses, but four of those eight were found to be smokers—personal communication from Humble). The age distribution for the female cases (controls) is as follows: age less than 65, 5 (74); age 65 or more, 15 (88).

250103218

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The odds ratio for the crude data on female never-smokers is 1.8 (90% C.I. = 0.6-5.4) for spousal smoking of cigarettes only and 2.3 (90% C.I. = 0.9-6.6) when spousal smoking also includes use of pipes and cigars. Based on mean cigarettes per day smoked by the spouse, the odds ratio of 1.2 at more than 20 cigarettes per day is somewhat lower than the odds ratio of 1.8 at the lower rate, less than 20 cigarettes per day. For duration of exposure, the odds ratio increases from 1.6 at less than 27 years to 2.1 at 27 or more years. It is reported that adjustment for age and ethnicity did not alter these results from the crude analysis. A trend test is included for duration of spousal smoking, but the sample sizes are too small to be meaningful. Application of logistic regression to adjust for variables gives values very close to the odds ratios for the crude analyses shown above for spousal smoking, for use of cigarettes only and also for combined use of cigarettes, cigars, and pipes.

The distribution of cases by cell type is given, but only with males and females combined. The ratios of ETS-exposed cases to the total, by cell type, are as follows: squamous cell (2/4), small cell (1/1), adenocarcinoma (either 6/12, 7/12, or 8/12), and others (either 3/3, 2/3, or 1/3, depending on correct ratio for adenocarcinoma).

The authors conclude that the results indicate increased risk from ETS exposure in never-smokers but not in active smokers.

A.15.3. Comments

This study evaluates smokers as well as nonsmokers for increased risk of lung cancer from spousal smoking. Not surprisingly, the number of smokers among the cases far outweighs the number of nonsmokers. No evidence of added risk to smokers from passive smoking is found. Such an evaluation, however, puts a great deal of faith in the exposure data and the power of statistical methods to detect what may be only a marginal increase in risk from ETS on top of active smoking.

Of more central concern to this review is the assessment of lung cancer from ETS exposure in never-smokers. The ETS data are taken from a larger study, so the matching no longer applies, although the adjustment for those variables (ethnicity and age category) in the analysis is worthwhile. The article suggests that the high rate of proxy response for cases in the original study (52%) may be due, at least in part, to inclusion of decedent cases. That topic is not explicitly addressed, however, and controls were not matched to cases on vital status. Never-smokers apparently may have a history of smoking, provided it is under 6 months' duration. Whether any never-smokers actually have a short smoking history is not discussed, but the never-smoker classification is less strict than in most studies.

250103182

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The data are evaluated a number of different ways, consistently yielding an increased odds ratio. The number of cases, however, is much too small (15 exposed, 5 unexposed) for the observed odds ratio to be close to statistical significance. Although similar values of the odds ratios might be observed in a larger study, that cannot be assumed. At most, the study outcome is suggestive of a possible association between ETS exposure and lung cancer occurrence, in need of additional support to be conclusive. Overall, this study is conducted well in many respects, but its contribution to the pool of evidence for assessment of lung cancer and ETS exposure is tempered by several weaknesses, as described above.

A.16. INOU

A.16.1. Author's Abstract

A case-control study on smoking and lung cancer in women was conducted in Kamakura and Miura, both in Kanagawa prefecture, Japan. The two cities are distinctly different in social environment; the former is a residential community, and the latter is a fishing village. After stratification on city and age groups, the odds ratio of lung cancer in nonsmoking wives was shown to be 1.58 when husbands smoked fewer than 19 cigarettes a day and 3.09 when husbands smoked 20 or more cigarettes a day. For comparison, the odds ratio for active smoking is 5.50. Although the study size is quite small, it provides additional evidence favoring the passive smoking and lung cancer hypothesis. (Paraphrased from author's discussion; no abstract was provided.)

A.16.2. Study Description

This study was conducted to assess the roles of active and passive smoking in the etiology of lung cancer in women. It is unclear how subjects or diagnoses were obtained, but cases are women who died of lung cancer in Kamakura or Miura in the time periods 1980-83 and 1973-81, respectively. Controls, consisting of women who died of cerebrovascular disease during the same time frames, are individually matched to cases on year of birth, year of death (± 2.5 years), and district of residence. It is not clear whether incident cases were used.

Face-to-face interviews were conducted by public health nurses and midwives. ETS subjects consist of the 28 nonsmoking cases and 62 nonsmoking controls remaining after elimination of 9 cases and 12 controls who were smokers. Husband's smoking status was not available for unspecified reasons in a total of 8 cases and 20 controls, but these figures include smokers as well as nonsmokers. The exact number of nonsmokers for which spousal smoking status was available is not specified but can be back-calculated from what is given (see below).

250103218

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

No information is given on the number of proxy respondents, the age distribution of the subjects, or attempts to confirm diagnoses of primary lung cancer.

The term "nonsmoker" is not defined, so it is not clear whether it refers to persons who never smoked or who do not smoke at present. Nonsmoking women whose husbands smoke at least five cigarettes per day are classified as exposed to passive smoking. Considerations of former smoking or marital status, ETS exposure at the workplace or in childhood, and duration of exposure are not addressed. No attempts to verify the reliability or validity of the data are mentioned.

The number of subjects is not delineated by case versus control and exposed versus unexposed figures. They can be determined from the odds ratio and confidence interval, however, as 18 out of 22 (exposed over total) cases and 30 out of 47 controls. For nonsmoking women with smoking husbands, the crude odds ratio calculated by the reviewers is 2.55 (95% C.I. = 0.74-8.78). (*Note:* OR = 2.25 is erroneously reported in the article. The OR value of 2.55 has been confirmed by Hirayama.) When husbands' smoking is divided into two strata (< 19 cig./day and 20+ cig./day), the odds ratios increase with exposure from 1.16 to 3.35, giving a statistically significant trend ($p < 0.05$). Age-adjusted odds ratios of 1.39 and 3.16 are reported for the two strata; adjustment for both age and district yields corresponding odds ratios of 1.58 and 3.09. (*Note:* The first OR value, 1.58, is incorrectly reported as 2.58. The value 1.58 has been confirmed by Hirayama.) The authors conclude that, although the study size is quite small, the results provide more evidence favoring the hypothesis that passive smoking causes lung cancer.

A.16.3. Comments

The number of subjects remaining after active smoking and missing data exclusions is small, guaranteeing poor power and lack of statistical significance in the absence of large odds ratios. The details on study design are limited. The source of cases and controls is not mentioned, for example, and it is unclear whether incident or prevalent cases were used.

Information regarding quality control and related concerns is equally sparse. Interviewers used standardized questionnaires, which would help to promote consistency, but no mention is made of blinding them to subject background or study question, the absence of which could introduce interviewer bias (probably in a positive direction). Because cases and controls are stated to have died during the study period, it is probable that proxy respondents were required, but the extent is unknown. In addition, neither duration of ETS exposure from spousal smoking nor exposure from other sources, such as other cohabitants, was considered. The resultant inaccuracy of exposure assessment probably biases the results toward the null. Lack of information on

250102184

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

former smoking status or verification of diagnosis may introduce biases of indeterminate direction. Except insofar as the district acts as a surrogate for factors related to socioeconomic status, no potential confounders other than age or district of residence were considered. The meaning of "nonsmoker" is not given. Was that status left to self-classification? Is some degree of past smoking acceptable? Is smoking history a factor at all (i.e., does nonsmoking refer simply to the current status)? Accurate and meaningful segregation of never-smoking subjects is needed for analysis, but there is no indication that that was accomplished.

Although a substantial odds ratio was observed for husband's smoking, these results are based on a small sample with too few details provided to assess adequately either the evidence or the study's design and execution. The numerous sources of potential bias are enhanced by the omissions or sketchy descriptions of the study. The statistical uncertainty of the odds ratios given is reflected in the extremely wide confidence intervals shown. The test for trend does not add any additional information. It is basically a restatement of the significant comparison between the heavily exposed group (husband smokes > 20 cig./day) and the unexposed group. Unfortunately, the brevity of the description of this study in the source available severely limits its utility.

A.17. JANE

A.17.1. Author's Abstract

"The relation between passive smoking and lung cancer is of great public health importance. Some previous studies have suggested that exposure to environmental tobacco smoke in the household can cause lung cancer, but others have found no effect. Smoking by the spouse has been the most commonly used measure of this exposure.

In order to determine whether lung cancer is associated with exposure to tobacco smoke within the household, we conducted a population-based case-control study of 191 patients with histologically confirmed primary lung cancer who had never smoked and an equal number of persons without lung cancer who had never smoked. Lifetime residential histories including information on exposure to environmental tobacco smoke were compiled and analyzed. Exposure was measured in terms of "smoker-years," determined by multiplying the number of years in each residence by the number of smokers in the household."

A.17.2. Study Description

This study was undertaken in New York State to clarify the role of exposure to tobacco smoke in the household as a possible cause of lung cancer among nonsmokers. Interviews were conducted with former as well as never-smokers initially (Varela, 1987), but because matching

250103218

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

was carried out on smoking status, only never-smoking case-control pairs were included in the analyses for this article. The study includes both males and females, which are combined in all of the analyses. There are 146 (45) female (male) pairs.

Cases are never-smokers aged 20 to 80 years newly diagnosed with lung cancer at 125 referral centers in New York from July 1, 1982, to December 31, 1984. Controls are cumulatively sampled never-smokers identified from files of the New York Department of Motor Vehicles. Controls are individually matched to cases on age (± 5 years), gender, and residence. In addition, the same interview type (proxy or direct) was used for controls as for their corresponding cases. Exposure data were collected face-to-face via standardized questionnaire by interviewers blind to the subject's status.

From the 439 case-control pairs interviewed, 242 pairs containing former smokers and 6 pairs with a mismatch on the source of response were excluded. Of the remaining 191 pairs used in the ETS study, interviews were conducted directly with the subjects in 129 (68%) and with proxies in 62 (32%) (if a proxy was interviewed for a case, then a proxy was used for the matching control as well). No demographic comparisons were provided for the ETS cases and controls. For the whole study including smokers, the mean age of cases and controls is nearly identical (67.0 and 68.1, respectively; Varela, 1987). Histological verification of diagnosis was obtained for all but five cases (for whom only clinical information was available) out of the initial population of 439.

Persons smoking no more than 100 cigarettes over the course of their lifetime qualified as never-smokers for this study. Cigar or pipe smoking was apparently not considered. Exposure to ETS was deemed to occur when a smoker lived in the subject's household at any time from infancy to adulthood. Both total household smoke exposure and spousal smoke exposure were determined. Preadult (before 21 years of age) and adult exposure were examined separately. Exposures were computed in units of "smoker-years," the total number of years lived with each smoker summed over smokers. In addition, pack-years were calculated for spousal smoking. Workplace exposure also was estimated by smoker-years, whereas exposure in social settings was estimated subjectively on a scale from 1 to 12 for each decade of life and summed. Exposure data were not checked, and marital status was not considered in the analyses. No information on tumor type or location was provided for the never-smoking population.

Preadult exposure to 24 or more smoker-years occurred in 52 (29) cases (controls) whereas 82 (94) were exposed to 1 to 24 smoker-years and 57 (68) were unexposed. Odds ratios were calculated using matched-pairs regression analysis. Preadult passive smoking yielded increasing odds ratio of 1.09 (95% C.I. = 0.68-1.73) for 1 to 24 smoker-years and 2.07 (1.16-3.68) for 25 or more smoker-years. The odds ratios for adult exposure are low but also increase—from 0.64 (0.34-

250103218

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

1.21) at 1 to 24 smoker-years to 1.11 (0.56-2.20) at 75 or more smoker years. The odds ratios for lifetime exposure increase from 0.78 (0.36-1.67) at 1 to 24 smoker-years to 1.80 (0.83-3.90) at 25 to 99 smoker-years and then dip to 1.13 (0.56-2.28) at 100 or more smoker-years. Spousal smoking was not significantly associated with lung cancer. In fact, when results were stratified by type of interview, proxy interviews yielded strong and, in some instances, statistically significant *negative* associations for spousal smoking, with odds ratios between 0.20 and 0.68 for ETS expressed in terms of present or absent, smoker-years, and pack-years of exposure. The odds ratios for direct interviews, in contrast, range from 0.71 to 1.10 and are uniformly higher than the odds ratios for corresponding proxy responses. Workplace exposure to 150 or more person-years yielded an odds ratio of 0.91 (0.80-1.04), whereas a social setting exposure score of 20 led to a statistically significant *decreased* odds ratio of 0.59 (0.43-0.81).

The authors conclude that they found a significant adverse effect of relatively high levels of exposure to ETS during early life (before age 21). For those who were exposed to 25 or more smoker-years in their first two decades of life, the risk of lung cancer doubled. By contrast, they found no adverse effect of exposure to ETS during adulthood, including exposure to a spouse who smoked. This lends further support to the observation that passive smoking may increase the risk of subsequent lung cancer, and it suggests that it may be particularly important to protect children and adolescents from this environmental hazard.

A.17.3. Comments

The number of never-smoking cases is relatively large, resulting in above-average statistical power for evaluation of ETS effects. Controls were matched to cases on smoking status, as well as the key demographic factors of age, gender, and neighborhood. Comparability of cases and controls was likely good, as evidenced by the similar mean ages for the total population, although no other comparative information is available. Interviews were ostensibly conducted blindly, thus precluding interviewer bias, but in view of the use of population-based, basically healthy controls, it is questionable that diagnostic blinding was effective. The study's matching on smoking status with subsequent retention of matching and use of matched-pairs analysis for ETS exposure effectively eliminates potential confounding by age, gender, or residence, and makes confounding by related factors (such as socioeconomic status) less likely. A rare feature is the use of matching on interview type (i.e., proxy or subject direct), thus eliminating potential confounding by this source. Comparison of spousal smoking results for direct and proxy interviews, however, indicates consistently lower estimated risks from proxies. This suggests that use of proxy respondents did not merely lead to increased random misclassification but might

2501032187

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

have biased the outcome toward a negative association. The authors posit that proxies of lung cancer patients may be more likely to underreport exposure than those of control subjects. Curiously, however, although the authors report that odds ratios "frequently differed according to type of interview," they do not specify how the odds ratios differed for exposure other than spousal smoking. Also, the composition of the proxy groups—relative proportions of spouses, other relatives, and friends or associates—is never discussed, leaving unexplored the possibility that misreporting by spouses of cases may lie at the heart of the observed discrepancy. It is also interesting that the outcome of self- versus proxy responses in this study is in the opposite direction of the findings in GARF. Diagnostic misclassification is unlikely, given the histological verification of nearly all cases.

The restriction of subjects to persons smoking no more than 100 cigarettes in their lifetime theoretically eliminates active smoking as a source of bias, although no verification of smoking status was undertaken. Consideration of potential sources of ETS exposure is commendably thorough, and the calculation of total years of living with smokers, regardless of relation to the smoker, as an index of household smoke exposure minimizes the possibility that any source (e.g., roommates) is overlooked. In contrast, the index of exposure in social settings is highly subjective, and persons more habituated to passive smoke may report a given exposure as less severe than persons less accustomed to smoke, thus creating a negative bias. The proportion of controls classified as exposed to ETS is 80%, which is high in comparison to other studies. This suggests that some exposed controls may have only minor exposure to ETS, making detection of an association (if present) less likely. Unlike almost every other ETS study, males and females are combined in the analysis and only the joint results are reported. Because there are 45 (146) pairs of males (females), the sample sizes are sufficient to warrant reporting odds ratios separately by sex and to test the hypothesis of no difference due to gender.

Lung cancer odds ratios for adulthood, lifetime, and spousal smoking are consistently well below one for low ETS exposure relative to nonexposure, as if exposure had a protective effect. Thereafter, however, the odds ratios associated with increasing levels of exposure are suggestive of an upward trend in response. Although we would not dismiss the occurrence of this outcome as attributable to chance alone, it is consistent with the baseline lung cancer mortality rate in the control population simply being higher than that of the case population for reasons other than exposure to spousal smoking. A pervasive (systematic) negative bias linked with exposure could also produce such an effect. Both of these contingencies are speculative, however, because there is no evidence in the article to support either, aside from the outcome of the data. Further fueling the speculation, however, are the markedly lower odds ratios obtained from surrogate responses,

250103188

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

indicative of some source of bias acting unequally on proxy and nonproxy sources. Also speculative is the idea that using predicted responses from a model that fits the data poorly might produce such an effect, but that level of detail is beyond the scope of most published articles, including this one. Some explanatory discussion by the authors on these issues, as well as *separation of the analyses by sex*, would enhance interpretation of results and facilitate comparison with results of other studies on females.

The authors' finding that exposure during childhood and adolescence appears to influence subsequent lung cancer risk more than exposure during adulthood raises some interesting possibilities. More time may be spent in proximity to a household smoker (particularly the mother), on average, in childhood than in adulthood. According to data presented by K.M. Cummings (Roswell Park Memorial Institute, Buffalo, NY) at the Science Advisory Board meeting on EPA's draft ETS report (U.S. EPA, 1990), on December 4-5, 1990, heavy childhood exposure is a better surrogate for total lifetime exposure than is spousal exposure. Also, early exposure may appear to become a risk, either due to a long latency period for lung cancer or, perhaps, due to increased susceptibility at an earlier age. The results suggesting an effect from early exposure but not from spousal smoking are more nearly atypical than reinforced by other studies, though, and the number of exposure sources considered raises the possibility that the strength of association seen for preadult exposure may be due to chance. However, after elimination of 78 pairs with incomplete marriage or household exposure data, the association persisted and was strengthened (OR = 2.59), arguing against chance as the major influence. It is unclear what role, if any, negative bias due to proxy respondents may have had in the nonspousal analyses.

In summary, the findings for preadult exposure are not readily attributable to chance or confounding, although some role of interviewer bias or unmeasured confounding factors such as diet cannot be ruled out. No association with lung cancer incidence is observed for spousal smoking. The authors conclude, however, that, spousal smoking aside, other sources of household ETS exposure support the conclusion that exposure to ETS can cause cancer. That conclusion is not unequivocal in our view. In general, the odds ratios (aside from preadulthood exposure) tend to be low but trend upward with exposure, exhibiting more of a patterned response than one might expect to see due to randomness. This is puzzling as there is no apparent source of bias and the study appears to have been conducted with considerable forethought and thoroughness. The only exception noted is the lack of separate analyses and comparisons of males and females. These concerns notwithstanding, the study is a useful addition to the literature on ETS exposure and lung cancer.

2501032189

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.18. KABA

A.18.1. Author's Abstract

"Among 2,668 patients with newly diagnosed lung cancer interviewed between 1971 and 1980, 134 cases occurred in 'validated' nonsmokers. The proportion of nonsmokers among all cases was 1.9% (37 of 1,919) for men and 13.0% (97 of 749) for women, giving a sex ratio of 1:2.6. Kreyberg Type II (mainly adenocarcinoma) was more common among nonsmoking cases, especially women, than among all lung cancer cases. Comparison of cases with equal numbers of age-, sex-, race-, and hospital-matched nonsmoking controls showed no differences by religion, proportion of foreign-born, marital status, residence (urban/rural), alcohol consumption or Quetelet's index. Male cases tended to have higher proportions of professionals and to be more educated than controls. No differences in occupation or occupational exposure were seen in men. Among women, cases were more likely than controls to have worked in a textile-related job (relative risk = 3.10, 95% confidence interval 1.11-8.64), but significance of this finding is not clear. Preliminary data on exposure to passive inhalation of tobacco smoke, available for a subset of cases and controls, showed no differences except for more frequent exposure among male cases than controls to sidestream tobacco smoke at work. The need for more complete information on exposure to secondhand tobacco smoke is discussed."

A.18.2. Study Description

In 1969, the American Health Foundation began interviewing newly diagnosed lung cancer patients with cancer at sites potentially related to tobacco use for a case-control study that is still ongoing (Wynder and Stellman, 1977). The current article considers the data on lung cancer in nonsmokers alone collected from newly diagnosed lung cancer patients between 1971 and 1980. Several factors are of interest: histology, demographic factors, residence, Quetelet's index, alcohol consumption, previous diseases, occupation and occupational exposures, and ETS exposure. The number of nonsmokers among the cases is small, so the authors consider the results to be preliminary.

The study from which the data on lung cancers in nonsmokers are extracted is a very large effort that includes tobacco-related cancers at multiple organ sites and includes smokers as well as nonsmokers. The cases are from approximately 20 hospitals in 8 U.S. cities (about one-third from New York City). With reference to the lung cancer cases in that study, histologic type of lung cancer was determined from pathology reports and discharge summaries. Secondary lung cancer cases were excluded. Controls consist of hospital patients with diseases unrelated to tobacco use who were pair-matched with cases on hospital, age (within 5 years), sex, race (with five

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

exceptions), date of interview (within 2 years), and nonsmoking status. Cases appear to be incident, and control sampling is density. All subjects were interviewed while patients were in the hospital. The questionnaire for the interviews was expanded in 1976. Questions on exposure to ETS were not included, however, until an addendum to the questionnaire in 1978, which was then modified in 1979.

The term "nonsmoker" applies to subjects who have smoked less than one cigarette, pipe, or cigar per day for a year. The term "never-smoker" is used interchangeably. Independent of the intended definition, however, subjects whose hospital charts indicated any record of smoking, even in the remote past, were excluded from the nonsmoker classification. ETS subjects include 53 (25) females (males), after combined attrition of 22 (9 without primary lung cancer and 13 with a record of smoking). The age distribution of the female cases (controls) is as follows: age less than 50, 12 (15); age 50 to 59, 26 (24); age 60 to 69, 29 (34); age 70 or more, 30 (24). Histologic data on lung cancer type are given for female cases: squamous cell (16), adenocarcinoma (60), alveolar (12), large cell (4), and unspecified (5). The authors report that exposed cases did not differ from the unexposed cases in the distribution of histologic type.

A person is "ETS exposed" (1) at home, if currently exposed on a regular basis to family members who smoke, (2) at work, if currently exposed on a regular basis to tobacco smoke at work, and (3) to spousal smoke, if the spouse smokes. There are data on 53 cases and their controls for exposure at home and at work, but data on only 24 cases and 25 controls for spousal smoking. This is because of the change in the questionnaire from 1978 to 1979 and because spousal smoking was only applicable for women currently married. Because nonsmoking status was a variable for matching, the 53 pairs of cases and controls for analysis of exposure at home or at work are matched; the data for spousal smoking, however, are technically not matched. There is no indication at all of an association between ETS exposure and lung cancer for women from exposure at home, at work, or from spousal smoking. For ETS exposure at home, there are 16 out of 53 (exposed/total) cases and 17 out of 53 controls; for exposure at work, the figures are 26 out of 53 cases and 31 out of 53 controls; and for spousal smoking, the data are 13 out of 24 cases and 15 out of 25 controls. No statistical calculations are provided for females. From cur calculations, the odds ratio for spousal smoking is 0.79 (95% C.I. = 0.25-2.45). (Among male subjects, exposure to ETS in the workplace was slightly significant, $p = 0.05$, as reported in the article.) For other potential risk factors for lung cancer in women other than passive smoking, it was found that cases were more likely than controls to have worked in a textile-related job (OR = 3.1; 95% C.I. = 1.1-8.6), but the significance of the finding was not clear. It was also found that more female

2501032191

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

cases had a history of pneumonia compared to controls, but no interpretation could be attached to the observation.

A.18.3. Addendum

Unpublished preliminary results of a study of ETS and lung cancer in never-smokers conducted at the American Health Foundation have been reported at two meetings—The American Public Health Association (APHA) 119th Annual Meeting, Atlanta, Georgia, November 10-14, 1991, and The Toxicology Forum, 1990 Annual Winter Meeting, Washington, D.C., February 19-21, 1990. A completed report for our review was not available at the cutoff date for inclusion in this document (personal communication with the first author, Dr. G.C. Kabat). Enclosed below is the abstract for the APHA meeting.

RISK FACTORS FOR LUNG CANCER IN LIFETIME NON-SMOKERS
Geoffrey C. Kabat, Ernst L. Wynder

> Risk factors for lung cancer in lifetime non-smokers (NS) were assessed in a hospital-based case-control study carried out between 1983 and 1990. The study population consisted of 41 male and 69 female NS cases and 117 male and 187 female NS controls matched on age, race, hospital, and date of interview. Evidence of an effect of exposure to environmental tobacco smoke (ETS) was inconsistent. In males, there was no difference between cases and controls in reported exposure to ETS (yes/no) in childhood, in nonsignificant association with exposure in childhood (OR = 1.6, 95% C.I. 0.9-2.8), but no association with exposure in adulthood at home or at work. Male cases were somewhat more likely to have a smoking spouse (OR = 1.6, 95% C.I. 0.7-3.9), whereas there was no difference in females. Cases and controls did not differ in reporting a history of previous respiratory diseases. Female cases were more likely to report a history of radiation treatment (OR = 4.3 95% C.I. 1.5-12.3). In females, but not in males, a significant inverse association was observed between body mass index (based on self-reported weight 5 years prior to diagnosis) and lung cancer risk.

A.18.4. Comments

Although the study contains more than 2,600 patients, only a small number of nonsmokers are available because questions about ETS exposure were not included in the interview until 1978 and the questions were changed in 1979. It is not clear just how the questionnaire was changed, although the general tenor of the article suggests care in study planning and execution. The design for the larger study from which the ETS data are taken is pair-matched on numerous factors of potential interest, including "nonsmoking status," which contributes favorably to the analysis of ETS data alone. Cases with secondary tumors were excluded, histological type was considered, and all subjects were personally interviewed. It appears that only the currently married females were included in the question regarding exposure to spousal smoke, which

250103192

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

alleviates the need to make some approximating assumptions regarding exposure of widows, singles, and so forth.

Two potential concerns about the analysis of ETS subjects have to do with the definition of "ETS exposure" and "nonsmoker." It is noted that duration of smoking was comparable in cases and controls, but interview questions regarding exposure to ETS refer only to current exposure (this is not explicit in the article but was confirmed by the first author). Also, this measure of exposure has no units (e.g., number of cigarettes per day or pack-years smoked by spouse), which might leave the question less subjective and perhaps help to dichotomize on ETS exposure more sharply. Because lung cancer may have a latency period of 20 years or so, exposure in the past, both in terms of duration and intensity, may be more meaningful than recent exposure. With regard to the definition of nonsmoker, the requirement is less rigid than is often imposed. Ever-smokers are included provided they did not smoke more than the equivalent of 1 cigarette per day for 1 year (about 18 packs). Smoking may seriously confound ETS exposure, and it is difficult to know what constitutes a "negligible" level of past smoking.

One of the factors of interest to the investigators is occupation, so cases and controls were not matched on that variable. For ETS exposure, occupation could be a potential confounding factor. Among females, the controls contain a higher percentage of professional and skilled workers than do the cases (47 to 25), and a lower percentage of housewives (41 to 50). Some differences are also apparent in religious preference between cases and controls that may bear some influence through lifestyle or dietary practices. Variables such as these may need to be taken into account in an adjusted analysis when more data become available.

As noted previously, this article is presented as a preliminary report, and it should be interpreted in that light. The data set on ETS subjects is small. We expressed some reservations about the operational meaning of "nonsmoker" and "ETS exposed," both of which could be more strict. Nonsmokers may have a light history of smoking; exposed nonsmokers may have very little history of exposure. Both factors may be sources of bias, the second one toward the null hypothesis of no effect, and the first one possibly in either direction. This study contributes some useful evidence for the epidemiologic evaluation of whether ETS poses a detectable lung cancer risk, but the potential for bias and the uncertainty due to small sample size could be influential.

A.19. KALA

A.19.1. Author's Abstract

"A case-control study was undertaken in Athens to explore the role of passive smoking and diet in lung cancer, by histologic type, in non-smoking women. Among 160 women with lung

250103219

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

cancer admitted to one of seven major hospitals in Greater Athens between 1987 and 1989, 154 were interviewed in person; of those interviewed, 91 were life-long non-smokers. Among 160 identified controls with fractures or other orthopedic conditions, 145 were interviewed in person; of those interviewed 120 were life-long non-smokers. Marriage of a non-smoking woman to a smoker was associated with a relative risk for lung cancer of 2.1 (95% confidence interval [CI] 1.1 — 4.1); number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data collected through a semi-quantitative food-frequency questionnaire indicated that high consumption of fruits was inversely related to the risk of lung cancer (the relative risk between extreme quartiles was 0.27 (CI 0.10 — 0.74). Neither vegetables nor any other food group had an additional protective effect; furthermore, the apparent protective effect of vegetables was not due to carotenoid vitamin A content and was only partly explained in terms of vitamin C. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent and did not confound each other. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma."

A.19.2. Study Description

This study was undertaken in Athens, Greece, in 1987-89. It sought to explore the role of passive smoking and diet in the causation of lung cancer in nonsmoking women. All data used in the study were collected specifically for that purpose.

Cases are never-smoking women hospitalized in one of seven Greater Athens area hospitals during an 18-month period of 1987-89 with a definite diagnosis of lung cancer from histologic, cytologic, or bronchoscopic exam. Controls were selected from female never-smoking patients in the orthopedic ward of the same seven hospitals and an orthopedic hospital. A control was interviewed within 1 week of a corresponding case, thus essentially density-sampled but otherwise unmatched. Cases were not specifically restricted to incident cancers. All subjects were interviewed face-to-face by one of five trained interviewers; interviews were apparently unblinded. A total of 160 lung cancer cases and an equal number of controls were initially identified; 6 cases and 12 controls were too ill to interview, whereas 3 controls and no cases refused to participate. After exclusion of smokers, 91 cases and 120 controls remained. The age distributions of the cases and controls are very similar: for cases and controls, 16.5% (14.2%) were less than 50 years of age, 19.8 (18.3%) were 50 to 59, 29.7 (25.8%) were 60 to 69, and 34.1 (41.7%)

250103219H

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

were 70 or older. Current residence, level of education, occupation (housewife vs. other) and marital status were also similarly distributed between cases and controls. Case diagnosis was established by histology (48%), cytology (38%), or bronchoscopy (14%), with exclusion of cancers diagnosed as secondary.

Persons reportedly smoking fewer than 100 cigarettes in their lifetime are classified as nonsmokers. No mention is made of pipe or cigar smoking. Several different sources of ETS exposure are considered: husbands who smoke quantified in terms of years exposed and average number of cigarettes smoked per day; household members *other* than husbands who smoke, quantified by the sum of years exposed to each smoker; and coworkers who smoke, measured by the number of smokers sharing the "same closed space" as the subject. Presumably childhood exposure is included in the household exposure assessment. For spousal smoking, single women are considered unexposed, whereas exposure of widowed or divorced women is based on their married period. No attempts to verify exposure are mentioned.

For analysis of husband's smoking based on cigarettes per day, 64 out of 90 (exposed/total) cases and 70 out of 116 controls gives a crude odds ratio of 1.6 for 90 cases and 116 controls; 64 cases and 70 controls were exposed. The authors present results stratified by four exposure categories, which indicate no significant association ($p = 0.16$). Crude data for husband's smoking stratified by five levels of smoking duration (never, < 20, 20-29, 30-39, and 40+ years) yield a marginally significant increase in association with increasing duration ($p = 0.07$), with odds ratios of 1.0, 1.3, 1.3, 2.0, and 1.9, respectively. No statistically significant association was noted for ETS exposure from other household members ($p = 0.60$) or for exposure at work ($p = 0.13$), but the crude odds ratios for these exposures were 1.41 and 1.39, respectively. Stratification by level of intake for each of 16 food and nutrient groups yielded a significant negative (favorable) association with cereals ($p = 0.04$) and a possible association with fruits ($p = 0.11$).

Multiple logistic regression was then used to adjust results for age, education, and interviewer. An adjusted relative risk estimate of 1.92 (95% C.I. = 1.02-3.59) was obtained for marriage to a smoker. After adjustment, trends for estimated lung cancer risk showed an increase with duration of exposure (average 16% per 10 years) and packs per day (6% per pack), but these were not statistically significant. No trend was observed for ETS in the household or workplace. Adjustment for other sources of air pollution had no effect on the analyses. Adjustment of dietary analyses for age, education, interviewer, and total energy intake indicated a significant decrease in estimated risk between highest and lowest quartiles of consumption of fruit (RR = 0.33; $p = 0.02$) and a nearly significant increase with consumption of retinol (RR = 1.31; $p = 0.06$), whereas beta carotene (RR = 1.01) and other dietary factors had no significant effect.

250103219S

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Adding fruit consumption to the model for passive smoking increased the adjusted relative risk for husband's smoking slightly, from 1.92 to 2.11. Stratification by lung cancer cell type yielded somewhat lower adjusted estimated relative risks for adenocarcinoma (2.04) than for squamous, small, and large cell cancer combined (2.58). No adjusted results were presented for other household or workplace exposure.

The authors' conclusion is best reflected in their abstract (shown in full above). Marriage of a nonsmoking woman to a smoker was associated with a relative risk for lung cancer of 2.1. Number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data indicated that high consumption of fruits was inversely related to the risk of lung cancer. Neither vegetables nor any other food group had an additional protective effect. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent and did not confound each other. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma.

It is noted that these findings are compatible with the relatively low incidence of lung cancer in the Greek population—a population with the highest per capita tobacco consumption in the world, but with a very high fruit consumption as well.

A.19.3. Comments

This study was generally well designed and executed. Set up specifically to address passive smoking and diet as etiological factors in lung cancer, it includes sufficient numbers of nonsmoking women to produce substantive results. Interviews were face-to-face and no proxies were used, enhancing accuracy and comparability of responses, whereas the very low rate of refusal minimizes potential bias due to volunteer selection. Cases and controls were very similar demographically, were drawn from most of the same hospitals, and were matched temporally on time of interview, so comparability seems high. Furthermore, the study hospitals' patient population accounts for the majority of lung cancer and trauma patients seen in the Athens area, enhancing generalizability of results. Most lung cancers were histologically or cytologically confirmed, reducing chances for misclassification of disease status.

On the debit side, the apparently unblinded interviews could have been biased (although what can be accomplished toward that end is limited). Adjustment for interviewer in the analyses did not affect the results, however, and it is unlikely that all interviewers would share the same

250103196

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

bias. Determination of what constitutes workplace exposure is vague, and childhood exposure is not clearly differentiated from adult household exposure; these were notably the passive smoking categories, which showed the least association with lung cancer. ETS exposure in the workplace is analyzed with regard to trend (Table 2), with levels of exposure represented by "housewife" (zero exposure), "minimal," and "some," resulting in a p value of 0.13. Perhaps correctly, the authors cautiously note the evidence that ETS exposure is associated with increased risk (referring to Table 2 in general, not just exposure at work) but indicate that the differences are not large enough to be interpretable without controlling for confounding effects. An analysis of exposed versus unexposed for the workplace may have been useful, especially an adjusted analysis. Our calculation of the crude odds ratio for a comparison of "minimal" and "some" exposure at work is 1.7, which is suggestive.

Methodological rigor and thoroughness are particularly evident in the treatment of potential sources of confounding. Despite the demographic similarity of cases and controls, the key demographic variables of age and education were nevertheless controlled for in the analyses, along with interviewer identity. Air pollution, total energy intake, and other dietary factors were also examined as potential confounders, and the impact of cancer type was evaluated. An association of husband's smoking with lung cancer yielding an odds ratio of around 2 persisted throughout. The authors claim to have taken special effort to exclude ex-smokers from misclassification as never-smokers, taking account of this potential source of upward bias. No discussion was found, however, of what measures were taken to control misclassification of former smokers as never-smokers, beyond interviewing subjects about current and former smoking habits.

In summary, this study presents evidence of a level- and duration-dependent association between husband's smoking and lung cancer in a well-defined and highly comparable group of Greek cases and controls. Positive but nonsignificant relationships with general home or workplace passive smoking were observed, and there are indications that additional analysis of workplace exposure may be worthwhile. No effect of air pollution was observed. With regard to dietary factors, the large number of potential factors considered raises the issue of multiple comparisons. Fruit consumption may be a significant factor, but further evidence is needed to firmly establish this, particularly in view of the number of dietary factors explored. Dietary factors, however, do not account for the results for ETS exposure in this study. The results regarding spousal smoking cannot be readily attributed to bias, and they provide good quantitative data on the issue of passive smoking and lung cancer. This well-conducted study makes a valuable contribution to the evidence on lung cancer and ETS exposure.

250103197

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.20. KATA

A.20.1. Author's Abstract

"It is becoming noticeable in Japan that with increased incidence of lung cancer, there has been an increase in pulmonary carcinoma in women. Active smoking by women is increasing, while concern over passive smoking has been intensifying, and the effect of passive smoking on carcinogenesis had become a social problem. Regarding this effect, immunological and public health reports have appeared in Japan, but there have been few clinical reports, and detailed analysis of patients has been inadequate. Lung cancer presents a variegated histological picture, and presumably there are different carcinogenic factors for different histological types, although there have also been few reports on this subject. The effect of passive smoking probably varies depending on the regional environment and custom, and these factors should also be analyzed and included in the investigation. The present report describes our findings regarding the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women."

A.20.2. Study Description

This study was undertaken in the Nara Prefecture, Japan, to investigate the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women. Active smokers are included in the study, from which the nonsmokers are drawn for analysis. Matching is retained, however, in the nonsmokers.

For the whole study, subjects were drawn from a hospital (presumably the Nara Prefecture Medical University Hospital) during an unspecified period of time. Cases are female patients with histologically diagnosed lung cancer; controls are female patients with "non-malignant" disease, matched 2 to 1 with cases on age plus or minus 2 years. It is not clear if only incident cases were used and if controls were density sampled. Case diagnoses were obtained from histological exam results, whereas control diagnoses were presumably from medical charts. Other information was collected from apparently unblinded "questioning," with an unspecified degree of reliance on proxy responses from family members.

A total of 25 cases and 50 controls are included in the study; no information on refusals is provided. Exclusion of active smokers leaves only 17 cases and, with retention of 1:1 matching, 17 controls. Mean ages for the total study population are 67.5 ± 8.8 years (67.6 ± 8.5 years) for cases (controls). The age distribution of ETS subjects is not discussed. Nonsmokers are defined by exclusion of "active smokers," with no delineation between former and current smokers. ETS exposure is defined as exposure to smoking more or less daily through living with a smoker. Three periods of ETS exposure are considered: current, past, and childhood, the last for those

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

"exposed since early childhood." Clearly these types are not mutually exclusive, although current sources of exposure are omitted from the "past" exposure category, even if present for a long time.

ETS exposure is quantified as cigarettes per day smoked times number of years. No mention is make of cigar or pipe smoking, nor of checks on exposure data. No distinction is made regarding marital status. Tumors occurring among current passive smokers were mostly adenocarcinomas (13/17), the remainder (4/17) being squamous or small cell cancers. Airway proximity was not specified. Excluding active smokers, all 17 cases were current passive smokers, compared to 14 out of 17 controls, for an odds ratio of 1.2, whereas past passive smoking characterized 16 of 17 cases and 17 of 17 controls, for an odds ratio of 0.9 (these odds ratios reflect the substitution of 0.5 for 0 in the exposure categories in which no subjects fall). Childhood passive smoking was reported in 13 of 15 cases and 7 of 15 controls (apparently all those for whom information was available), for an odds ratio of 7.4 ($p < 0.1$). None of the passive smoking odds ratios was statistically significant at the 5% level. No definite conclusion can be drawn from the present study, but there is a suggestion that passive smoking is associated with development of lung cancer in the Nara region. The effect of passive smoking that continued to the present time was especially marked, particularly in squamous cell carcinoma and small cell carcinoma. With adenocarcinoma, an effect of passive smoking in the past is suspected. Along with passive smoking, the association of some intrinsic factor (genetic tendency) to varying degrees in the different histologic types of lung cancer in women, especially in adenocarcinoma, is apparent.

A.20.3. Comments

The histological diagnosis of all cases, in combination with the apparent involvement of the researchers in the diagnoses, virtually eliminates the potential pitfall of misclassification of lung cancer cases. It also allows specific breakdowns by cell type. With regard to passive smoking, however, limitations related to exclusion of active smokers greatly reduced the study's potential.

In their initial analyses, the authors investigate passive smoking without excluding or stratifying on active smoking and report statistically significant associations with lung cancer and combined effects with family history of cancer. This is not a meaningful analysis, because the effects of active and passive smoking cannot be separated and because passive smoke exposure probably correlates strongly with extent of active smoking. Excluding active smokers greatly reduces the available numbers of matched subjects and, in combination with the very high exposure prevalence among qualifying controls, makes the differences between cases and controls

250103219

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

highly unstable for all comparisons except for that of childhood exposure. Even here, with an estimated relative risk of 7.4, the results do not reach the 5% level of statistical significance, notwithstanding the problem of multiple comparisons. This does not deter the authors from attempting cell-type-specific analyses, but these too fail to yield significant results. The extraordinarily high proportion of exposed present and past passive smoking controls is apparently a fluke, because the proportion is not as high in the total control subject population (or childhood passive smoking controls). Nevertheless, exposure was very common among controls. This indicates that the exposure criteria may be too lax or, alternatively, that the control population included a substantial proportion of persons with smoking-related diseases (controls being only stipulated not to have malignant disease).

In light of the minimal utility of the study's passive smoking analyses, detailed consideration of design strengths and weaknesses is unwarranted. Major points not already mentioned relate to information ascertainment and confounding. Interviews were apparently unblinded and, especially if conducted by the authors themselves, may thus have been biased toward uncovering exposure among cases (although the high prevalence of exposure among controls as well as cases argues against this). Furthermore, the extent of proxy interviews, potentially decreasing accuracy of exposure assessment, is unclear.

All subjects are female and, although results are not age adjusted, matching on age was retained for all analyses. No other potential confounders except family history of cancer were considered, probably due to limited subject numbers, because much information on potential confounders was collected. Moreover, family history was considered only in the nonmeaningful analyses, which did not differentiate active and passive smokers. Thus, although the problems with numbers and exposure misclassification probably reduced the study's ability to detect whether an association exists, information bias and confounding could have biased results either up or down.

In summary, this study's data are consistent with an association of passive smoking, particularly childhood exposure, with lung cancer, but the results are too unstable and subject to potential bias to carry much weight, and the quantitative results must be viewed with extreme caution.

A.21. KOO

A.21.1. Author's Abstract

"Lifetime exposures to environmental tobacco smoke from the home or workplace for 88 "never-smoked" female lung cancer patients and 137 "never-smoked" district controls were

05/15/92
250103220

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

estimated in Hong Kong to assess the possible causal relationship of passive smoking to lung cancer risk. When relative risks based on the husband's smoking habits, or lifetime estimates of total years, total hours, mean hours/day, or total cigarettes/day, or earlier age of initial exposure, were combined with years of exposure, there were no apparent increases in relative risk. However, when the data were segregated by histological type and location of the primary tumor, it was seen that peripheral tumors in the middle or lower lobes (or less strongly, squamous or small-cell tumors in the middle of lower lobes) had increasing relative risks that might indicate some association with passive smoking exposure."

A.21.2. Study Description

This study, the second of four from Hong Kong, is based on a secondary data set of reported female never-smokers. The parent study from which the data on ETS subjects was drawn includes ever-smokers in a matched case-control study of 200 cases and 200 controls (Koo et al., 1984; also see Koo et al., 1983). Its objective is to assess the role of passive smoking as a potential etiological factor in the high incidence rate of lung cancer among Chinese females in Hong Kong. The current article emphasizes the quantitation of lifetime ETS exposure and the histological profile of lung cancer in exposed never-smokers.

In the parent study, cases are from the wards or outpatient departments of eight hospitals in Hong Kong during 1981-83. Controls are healthy subjects from the community, matched on age (within 5 years), district of residence, and type of housing (public or private). The cases are incident, and control sampling is density. Attrition due to selection or follow-up totals 26 (8 too ill to interview and 18 with secondary lung cancers), leaving 200 cases for interview. Face-to-face interviews of 1.5 to 2 hours were conducted directly with cases and controls. There was no restriction of cases by cell type of lung cancer. The ETS subjects extracted from the parent study include 88 cases and 137 controls. Of the 88 cases, 83 were confirmed by histology and 5 were "confirmed malignant." The number of squamous cell and small cell cases combined is 32 (23 ETS exposed; 72%); the corresponding figure for adenocarcinoma and large cell combined is 44 (31 ETS exposed; 70%); 12 cases are of another cell type, or otherwise unspecified. For the 86 cases with available information, tumors were centrally located in 37 (25 ETS exposed; 67%) and peripherally in 46 (34 ETS exposed; 74%).

The term "never-smoker" applies to persons who have smoked a total of fewer than 20 cigarettes. Interview questions regarding exposure to ETS include cigarette and cigar smoking in the home during childhood, by the spouse and other cohabitants in adulthood, and workplace exposure. "ETS exposed" is technically used in several ways. For the comparison of exposed with

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

unexposed ever-marrieds, it means the husband ever smoked in the wife's presence. For measures of exposure in terms of duration or rate (e.g., total years, hours/day, total hours, and cig./day), there is some variation. For example, total years of exposure is derived by adding the years during which tobacco exposure occurred in the home or workplace. The total hours of exposure are calculated by multiplying the average hours per day of exposure by the years of exposure from each household smoker, or the amount of exposure at each workplace. The mean hours per day of exposure are found by adding the hours per day of home and workplace exposures and dividing this figure by the age of the subject. This figure is intended to approximate the average number of hours of exposure per day experienced by the subject, over her lifetime. Cumulative exposure is estimated by the total cigarettes smoked by family members, weighted by years of exposure.

When data are analyzed on the simple basis of whether a husband ever smoked in the presence of the wife, the crude and adjusted odds ratios are 1.55 (95% C.I. = 0.94-3.08) and 1.64 (95% C.I. = 0.87-3.09), respectively. The crude analysis applies to ever-marrieds only, which excludes three subjects. An adjusted analysis uses cigarettes per day smoked by the husband as the measure of ETS exposure. Conditional logistic regression was applied with stratification on district of residence and housing type (public/private); model parameters were included for age, family history of lung cancer (yes/no), number of live births, and number of years since exposure at home or in the workplace.

The crude and adjusted methods give very similar odds ratios and confidence intervals, but the tests for trend differ substantially. The test for trend on the crude data is based on the Mantel-Haenszel test, using midpoints of the intervals for cigarettes per day smoked by the husband; the significance value is $p = 0.10$. The p value for trend in the adjusted analysis is 0.32. For analysis of data by other measures of exposure, as described above, the estimated odds ratio ranges between 1.0 and 4.1 across the three levels of the various measures of ETS exposure for both the analyses of the crude data and the adjusted analyses by conditional logistic regression, with two exceptions from analysis of the crude data for hours per day of exposure. The results are not statistically significant in most cases, because the sample sizes at each exposure level are small. The dose-response patterns observed are clearly sensitive to the measure of ETS exposure used, with several exhibiting an apparent peak at a low exposure level. Although the authors acknowledge that it was troubling to find the lack of a response pattern, no further explanation is given.

The authors did not detect a significant trend in the crude or adjusted odds ratio for the four lifetime measures of passive smoking (total years, hours, mean hours/day, cig./day). Although the odds ratio for the intermediate level exposures of hours per day and cigarettes per

2501032202

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

day was significant, the odds ratio at the highest levels of exposure for these two variables fell to a nonsignificant 1.0 to 1.2. In fact, the odds ratio for the highest exposure levels for three out of the four measurements were below all of those with lower exposures and ranged from a very weak 1.0 to 1.4. On the other hand, most of the crude and adjusted odds ratios were greater than 1.0. Measurements based on increasing intensity of exposure, defined as increasing years (or hours, or cig./day) by mean hours per day of exposure, also did not indicate a dose-response relationship. The analysis of total years of exposure with age of exposure did not suggest that earlier age of initial exposure and increasing years of exposure led to higher odds ratios.

It is concluded that when the lung tumors were segregated by histological type and location, the resulting analyses showed that peripheral tumors in the middle or lower lobes, and squamous or small cell tumors in the same lobes, exhibited better odds ratio patterns for passive smoking in terms of consistency, strength, and dose-response. The odds ratio for total years, hours, and hours per day measurements of squamous and small cell lung tumors indicated consistently elevated risks with increasing exposure. This pattern was not found for any of the adjusted odds ratios for adenocarcinoma or large cell lung cancers.

The cases are divided into two groups histologically, those with squamous cell or small cell tumors, and those with adenocarcinoma or large cell malignancies. Although none of the crude or adjusted analyses are found to be significant, it is concluded that an observed dose-response pattern seems to be more apparent in the squamous or small cell group. With regard to tumor location, some evidence suggests that peripheral tumors in the middle or lower lobes may be more common in passive smokers.

A.21.3. Comments

As described above, the data employed in the current study were taken from a larger retrospective study of female lung cancer in Hong Kong (Koo et al., 1984) that matched 200 cases and controls on age, district of residence and housing type (private or public, an indication of socioeconomic status). Attention to detail and accuracy is evident in most aspects of the parent study. In particular, considerable effort was put into attempting to ascertain a better quantitative measure of exposure than used in preceding studies of ETS. Records were apparently verified to the extent possible to cross-check the accuracy of information collected, cancers were verified histologically, and analyses investigated questions related to the histological types and sites of tumors that may be related to passive smoking.

The never-smokers from the parent study, 88 cases and 137 controls, compose the secondary data set on which the current article is based. The matching of the subjects, of course,

25010322O3

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

is no longer assured, leaving the comparability of the two groups uncertain. In addition, 60 (27%) of the subjects are widows, with no information provided on the distribution between cases and controls. Because spousal smoking is typically the variable on which ETS exposure pivots, this may have some bearing on the response. An adjustment is made in some analyses for years since exposure to cigarette smoke ceased, but no information is provided to describe or support the assumptions used to do that.

Some factors in the study itself may be contributing to the variable dose-response patterns. First, the number of ETS subjects is fairly small. When the subjects are classified into finer categories of exposure, the statistical variability is greatly increased (total cases and controls is below 60, on average). Second, questionable measurements of ETS may be causing some distortion. For instance, in the calculation of total years and total hours of ETS exposure, the years and hours were not added for simultaneous exposure to more than one smoker or for concurrent exposure in the home and workplace. Pipe smoking and the cigarette consumption levels of coworkers were excluded from the weighted average of the total cigarettes per day smoked by each household member. Additionally, the mean hours per day of exposure were derived by adding the hours per day of home and workplace exposures and dividing this figure by the *age* of the subjects. Thus, measurement appears to be based on the assumption that never-smoking women were exposed to ETS evenly throughout their lives (the authors claim that only subjects were used for which the exposure remained relatively regular during the lifetime, although no mention was found of cases being omitted because of failure to satisfy this criterion). Even if this assumption were valid, childhood and adulthood exposures are mixed as if the effects of exposure are interchangeable. Interestingly, differences between exposure in childhood and adulthood is one of the questions addressed in the article.

Although the objective is worthy, the attempt to quantitate exposure more precisely than previous studies appears to obscure more than to clarify. Assumptions are not made very explicit and their potential implications are not addressed well, which leaves some uneasiness about the conclusions. The authors have published at least three articles before this study that have some bearing on passive smoking and lung cancer, but their results are not discussed in the current study, even when the data analyzed are from the same source (Koo et al., 1983; Koo et al., 1984; Koo et al., 1985). Those articles, one of which describes the parent study (the 1984 citation), appear to reach somewhat different conclusions from this study regarding the predominance of histological type associated with passive smoking. Putting the current study's conclusions within the context of related prior work would enhance their clarity and interpretation.

05/15/92
2501032204

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Considering the reservations described above, the suggestion that the evidence indicates some association of passive smoking with the *location* of tumors is an overinterpretation of the data. A weaker conclusion is warranted, namely, that ETS exposure is associated with increased lung cancer incidence. What may be of most value in this study is the analysis based on the dichotomous classification of cases and controls as exposed or unexposed based on spousal smoking. Two concerns, however, will be reiterated. The ETS data are taken from a larger study not matched on smoking status, so they are unmatched. The study includes 80 widows, without mention of their distribution between cases and controls. In the adjusted analysis, an attempt is made to take into account the number of years since last exposure, which would require some assumption regarding the change of risk relative to cessation of exposure. Both of these concerns are mitigated, however, by the similarity of the odds ratios and confidence intervals for the unadjusted and adjusted analyses. The care and thoroughness of the study in general make the results on the odds ratio for exposure to spousal smoke a useful contribution for evaluation with other study outcomes.

A.22. LAMT

A.22.1. Author's Abstract

"In a case control study in Hong Kong, 445 cases of Chinese female lung cancer patients all confirmed pathologically were compared with 445 Chinese female healthy neighborhood controls matched for age. The predominant histological type was adenocarcinoma (47.2%). The relative risk (RR) in ever-smokers was 3.81 ($P<0.001$, 95% CI = 2.86, 5.08). The RRs were statistically significantly raised for all major cell types with significant trends between RR and amount of tobacco smoked daily. Among never smoking women, RR for passive smoking due to a smoking husband was 1.65 ($P<0.01$, 95% CI=1.16, 2.35), with a significant trend between RR and amount smoked by daily by the husband. When broken down by cell types the numbers were substantial only for adenocarcinoma (RR=2.12, $P<0.01$, 95% CI=1.32, 3.39) with a significant trend between RR and amount smoked daily by the husband. The results suggest that passive smoking is a risk factor for lung cancer, particularly adenocarcinoma in Hong Kong Chinese women who never smoked."

A.22.2. Study Description

This hospital-based case-control study was conducted in Hong Kong in 1983-86, to investigate whether smoking is a major risk factor for lung cancer in Hong Kong Chinese women and, if so, to determine the relationship between smoking and the histological types of lung

05/15/92
250103220S

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

cancer. Both active and passive smoking are of interest. The ETS subjects constitute only a subset of the whole study, because it includes active smokers.

Eligible cases for the whole study are the 445 female patients with pathology-verified lung cancer admitted into eight large hospitals in Hong Kong during 1983-86. Cases were interviewed in person. Only a few eligible patients declined or were too ill to cooperate. An equal number of healthy neighborhood controls were identified and interviewed by density sampling. Controls were matched to cases on sex, age (± 5 years), and place of residence. The cases and controls include both never-smokers and ever-smokers, but smoking status was not used in matching. "Never-smoker" means a person who never smoked as much as one cigarette per day, or its equivalent, for as long as 1 year.

A woman is "ETS exposed" if her husband smoked for at least 1 year while they lived together. If the husband was an ever-smoker, information on the type of tobacco and amount usually smoked per day by the husband and the duration of exposure was obtained. No information was collected on ETS exposure from other household members' smoking or smokers at work. Single (never married) women were classified as nonexposed (6.8% and 5.2% in cases and controls, respectively). The treatment of widowed and divorced subjects is not explicitly addressed. Age and place of residence, as well as a series of other demographic variables, are similar between cases and controls.

The distribution of lung cancer by cell type in ETS cases is as follows: squamous cell, 12 out of 27 (number exposed/total); small cell, 6 out of 8; adenocarcinoma, 78 out of 131; large cell, 7 out of 9; and others or unspecified, 12 out of 24. The corresponding crude odds ratios and 95% confidence intervals are 0.85 (0.35-2.06), 3.00 (0.53-16.90), 2.12 (1.32-3.39), 3.11 (0.50-19.54), and 1.08 (0.41-2.82), respectively. The odds ratio for all cell types combined is 1.65 (1.16, 2.35), based on 115 out of 199 (exposed/total) cases and 152 out of 335 controls. The data for all cell types together, and for adenocarcinoma alone, are both significant at $p < 0.01$. No information is available on the airway proximity of tumors.

Trend tests were conducted for the amount smoked daily by the husband, categorized in terms of cigarettes as "nil," 1 to 10, 11 to 20, and 21 or more. The odds ratios in the three exposure categories are 2.18, 1.85, and 2.07, respectively, when all cell types are included. For adenocarcinoma alone, the corresponding odds ratios are slightly higher (2.46, 2.29, and 2.89). The dose-response relationship does not appear to increase between the lowest dose and the highest dose, but a test for trend is significant ($p < 0.01$ for all cell types and $p < 0.001$ for adenocarcinoma alone) when the "nil" group is included. No adjusted analyses are given.

05/15/92
250103220

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The authors conclude that the significant trends observed between relative risk and amount smoked daily by husband, for all cell types combined and for adenocarcinoma alone supports the view that the observed association between ETS exposure and lung cancer is likely to be causal.

A.22.3. Comments

This study is the fourth of the Hong Kong epidemiologic inquiries into tobacco smoke as a possible etiological factor in the high rate of lung cancer, particularly adenocarcinoma, among women. Active smoking was included as well as passive smoking because the previous studies in Hong Kong were inconclusive. According to the authors, this led to the hypothesis that smoking is not a risk factor for adenocarcinoma in Hong Kong Chinese women. Matching of controls to cases was conducted for the whole study, including active smokers. It cannot be assumed, however, that the never-smokers alone, who constitute 45% of the cases and 76% of the controls, are matched.

Overall the study demonstrates care in planning and execution. The sample size of ETS subjects is moderately large, providing higher statistical power than the previous Hong Kong studies. All cases were pathologically confirmed as primary lung cancers, essentially eliminating the potential for error due to disease misclassification. Odds ratios were calculated by histological type for comparison. Cases and controls were interviewed personally, apparently with no proxy respondents and very few refusals, which reduces the potential for response bias. The exclusive use of incident cases helps to control potential selection bias, and density sampling of controls contributes to comparability of cases and controls. For the whole study, including smokers, healthy controls were matched to cases by sex, age, and neighborhood of residence. The mean and standard deviation of ages are nearly identical in cases and controls. According to the authors, a comparison by other demographic variables showed that, for the whole study, cases and controls were also comparable in place of birth, duration of stay in Hong Kong, level of education, marital status, and husband's occupation. Further attention to detail is evident in the clear definitions of "never-smoker" and "ETS exposure," essential to accurate classification of subjects for analysis and interpretation. Single women were treated as not exposed to husband's smoking, which could be a source of bias because these women may be exposed from other household members. This possibility was considered, however, because the article reports that similar results were obtained when single women were excluded.

In summary, the crude odds ratios vary between 2.1 and 3.1 for small cell carcinoma, adenocarcinoma, and large cell carcinoma, with adenocarcinoma significant at $p < 0.01$. The odds

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

ratios are consistently elevated at all three intensity levels of spousal smoking, varying between 1.8 and 2.9, with the odds ratio for adenocarcinoma alone somewhat higher than for all cell types combined. There is no apparent upward trend, however, from the lowest smoking intensity (1-10 cig./day) to the highest (21+ cig./day). These statistical results are ostensibly suggestive of an association between ETS exposure and lung cancer incidence, but they are based on only crude data with cases and controls unmatched, even on ages. Nor are statistical methods used that could adjust for matching variables, or other factors, in the data analysis (e.g., by stratification or logistic regression). Although this study was carefully conducted in most respects, the disregard for potential confounding effects leaves the authors' conclusion uncertain.

A.23. LAMW

(*Note:* This study is part of the thesis of LAM Wah Kit submitted to the University of Hong Kong for the M.D. degree in 1985, entitled "A Clinical and Epidemiological Study of Carcinoma in Hong Kong." The description given below is from Chapter 7 of the thesis only, entitled "Case-Control Study of Passive Smoking, Kerosene Stove Usage, and Home Incense Burning in Relation to Lung Cancer in Nonsmoking Females (1981-84)," which the author submitted in response to our request. The abstract below was prepared by the reviewers, since none was available from the author.)

A.23.1. Abstract

The study's objective is to investigate the hypothesis that an inhaled carcinogen may be related to the high incidence of centrally situated adenocarcinoma of the lung observed in nonsmoking female patients. Air pollution is probably not an important factor because it presumably affects both men and women. Most women in Hong Kong either stay at home or join the work force in commerce, services, or manufacturing, which are not associated with any known risk factor for lung cancer. Three etiological activities, all predominantly in the home, are considered in this study: passive smoking, kerosene stove cooking, and home incense burning. No evidence was found to implicate exposure to kerosene stove fumes or incense burning in centrally located adenocarcinoma. There is suggestive evidence of an association between ETS exposure from smoking husbands and occurrence of peripheral (but not central) adenocarcinoma. Why the location tends to be peripheral instead of central is speculative.

250103208

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.23.2. Study Description

(*Note:* The details of the study are not complete in the material provided. Some useful information, however, is available.)

The cases are all of the Chinese female patients admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, between January 1981 and April 1984 with histologically and/or cytologically confirmed carcinoma of the lung of the four major cell types. Care was taken to exclude patients with secondary carcinoma of the lung; otherwise, all patients were included. The controls are Chinese female patients admitted to the orthopedic wards of the hospital in the period 1982-84, comparable to lung cancer patients in age and social class. Patients with pathological fractures due to smoking-related malignancies, or peripheral vascular disease-related orthopedic conditions were excluded.

Both cases and controls were patients of the third-class general wards, mostly from the lower income group. All subjects were interviewed in person. The questions covered dialect group, occupation, smoking habits, passive smoking, domestic cooking with kerosene, and home incense burning, in the form of a standardized questionnaire. For very ill patients, or for patients who spoke a dialect other than Cantonese or Mandarin, the next-of-kin was interviewed, with the patients as interpreter. The whole study, including active smokers, contains 161 cases and 185 controls, similar in age (median age is 67.5 [66] for cases [controls]), socioeconomic status (as measured by occupation and years of schooling), and recent residence. The author considered it unnecessary to stratify on these or any other variables.

The ETS subjects consist of 75 (144) cases (controls), including 16 (14) never-married cases (controls). The distribution of cases by cancer cell type is as follows: squamous cell (7), small cell (3), large cell (5), and adenocarcinoma (60). Questions related to ETS exposure include details on each smoker in the home (husband, others, mother, and father), amount smoked per day, hours of ETS exposure per day, and number of years smoked. Information about exposure in the workplace includes size of the workplace, number of coworkers who smoke, exposure time/day, and number of years of exposure at work.

Only the data for adenocarcinoma, the predominant cell type observed and the pathogenesis of interest, are analyzed. The number of cases is 37 out of 60 (exposed/total), and the number of controls is 64 out of 144, where ETS exposure refers to spousal smoking. The odds ratio (calculated by the reviewers) is 2.01 (95% C.I. = 1.09-3.72). The author divides the cases by location according to airway proximity, with 18 out of 32 (exposed/total) located centrally and 19 out of 28 in peripheral regions. The respective risk ratios are 1.61 and 2.64. Two tests were conducted for significance, including the Bayesian risk ratio analysis and a test of the slope for

250103220 9

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

the exposure parameter in a simple logistic regression model. The significance levels are 0.11 and 0.19, respectively, for the central location, and 0.01 and 0.02, respectively, for peripheral tumors. The test results differ widely for total passive smoking (home or workplace). For the central location, the respective significance levels are 0.09 and 0.3; for peripheral locations, the corresponding values are 0.03 and 0.15. It is suggested that the different outcomes for the two tests applied to total passive smoking may be due to a nonlinear logistic dose-response curve or to errors in assessing the level of exposure due to incomplete information. The apparent association between passive smoking and peripheral adenocarcinoma (and not central tumors) in the cases was unexpected. Based on the available raw data, exposure to a smoking spouse, cohabitant, and/or coworker is associated with an odds ratio of 2.51 (95% C.I. = 1.34-4.67) for all cell types combined. The author concludes that there is a suggestion of passive smoking associated with peripheral adenocarcinoma, particularly passive smoking attributable to smoking husbands. Kerosene and incense burning were not found to be associated with adenocarcinoma, either central or peripheral.

A.23.3. Comments

Cases and controls appear to be comparable in age, socioeconomic status, and recent residence for the whole study (including active smokers), although the study design is not matched on these or other variables. Some discrepancies between cases and controls are apparent, however, such as a higher percentage of cases than controls working outside the home (41% compared to 28%). The figures for nonsmokers alone (i.e., the ETS subjects) are not given, so comparability is uncertain for analysis of ETS exposure. Care has been taken to include only primary lung cancer patients among the cases, essentially eliminating this potential source of bias. Subjects were personally interviewed, with apparently only a small number of proxy respondents required, although no figure is given. The interviews were apparently not blinded, but that may have not been feasible considering the nature of the questions asked and the use of noncancer patients as controls. Considerable attention is given to histological type of cancer and the location in terms of airway proximity.

The author is particularly interested in the etiology of adenocarcinoma and focuses discussion on the adenocarcinoma cases to the exclusion of others. Although the raw data pertaining to other cell types are tabulated, more attention to those types in the analyses would have been useful. The adenocarcinoma cases are categorized further by central and peripheral location, which are analyzed separately. Again, a combined analysis would be useful (the reviewers calculated the crude odds ratio for the combined data, which is given above). Although

250103221O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

logistic regression is employed as one of the two statistical tools for analysis, factors that may differ between cases and controls are not included. Potential confounding variables need to be controlled for, by logistic regression, poststratification, or otherwise. To claim that cases and controls are similar in potential confounding characteristics does not alleviate the need to adjust for them in the analysis, particularly when the ETS data are a subset of the larger data set to which reference is made. Similarly, in testing three factors for an association with lung cancer (passive smoking, cooking with kerosene, and burning incense), it would be useful to conduct an analysis that will allow evaluation of the effect of each after adjustment for the other two.

The suggestive evidence that passive smoking is more likely associated with adenocarcinoma in peripheral rather than central locations may be logical but is weak, especially considering the lack of analytical rigor. The ratio of ETS-exposed cases of adenocarcinoma to the total is 18 out of 32 (56%) for central locations and 19 out of 28 (68%) for peripheral locations. This difference is not statistically significant ($p = 0.26$ by Fisher's exact test). Consequently, the "apparent association" between passive smoking and peripheral adenocarcinoma (and not central tumors) may well be due to chance alone. There is suggestive evidence in the data that passive smoking may be associated with lung cancer (OR = 2.01, $p < 0.03$ for a one-sided test), but that is based only on the crude odds ratio in unmatched data and needs to be confirmed by a more thorough evaluation of the data that takes potential confounders into account. Overall, this study provides some suggestive evidence for an association between passive smoking and lung cancer. Potential confounders (including age) have not been controlled for, however, so attribution of the elevated odds ratio to ETS exposure is uncertain.

A.24. LEE

A.24.1. Author's Abstract

"In the latter part of a large hospital case-control study of the relationship of type of cigarette smoked to risk of various smoking-associated diseases, patients answered questions on the smoking habits of their first spouse and on the extent of passive smoke exposure at home, at work, during travel and during leisure. In an extension of this study an attempt was made to obtain smoking habit data directly from the spouses of all lifelong non-smoking lung cancer cases and of two lifelong non-smoking matched controls for each case. The attempt was made regardless of whether the patients had answered passive smoking questions in hospital or not.

Amongst lifelong non-smokers, passive smoking was not associated with any significant increase in risk of lung cancer, chronic bronchitis, ischemic heart disease or stroke in any analysis.

250103221

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Limitations of past studies on passive smoking are discussed and the need for further research underlined. From all the available evidence, it appears that any effect of passive smoke on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist at all."

A.24.2. Study Description

This study was undertaken in England, essentially from 1979-83. Its stated objective is to investigate the relationship between passive smoking and risk of lung cancer in nonsmokers. It is an outgrowth, however, of a hospital-based case-control study to assess whether the risk of cardiorespiratory disease associated with smoking varies by type of cigarette smoked. It was initiated in 1977 in 10 hospital regions in England. In 1979, interviewers began gathering information on passive smoking as well in four of the regions. Then in 1982, this case-control study of the effects of passive smoking was begun using nonsmoking cases identified by the ongoing cardiorespiratory effects study. For the new study, spouses of cases and specially selected controls were interviewed regarding smoking habits. Previously collected data on passive smoke exposure obtained from patients back to 1979 were used.

Basically, two substudies were conducted. One used the data obtained directly from hospitalized cases and controls to address several sources of passive smoke, including spousal (henceforward the "passive smoking" study); the second substudy used data obtained from the *spouses* of cases and controls along with corresponding information from the patients themselves, when available, to address spousal smoke exposure only (henceforward the "spousal smoking" study). Cases for the passive smoking substudy were currently married lifelong nonsmokers diagnosed with lung cancer (of any cell type), chronic bronchitis, ischemic heart disease, or stroke in one of four participating hospital regions. Controls were currently married lifelong nonsmoker inpatients diagnosed with a condition definitely or probably not related to smoking and individually matched on sex, age, hospital region, and, when possible, hospital ward and time of interview. Thus, density sampling was used when possible. For the spousal smoking substudy, previously married patients were excluded; the same criteria otherwise applied, except that controls were now matched on sex, age decade, and—as far as possible—hospital and time of interview.

Diagnoses were obtained from medical records. Exposure data were obtained through apparently unblinded, presumably face-to-face interviews with inpatients and their spouses. A total of 3,832 married cases and controls were interviewed regarding passive smoking through 1982; it is unclear how many potential subjects refused or died before interview. Only 56 of these

250103212

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

were married lung cancer cases meeting the spousal smoking study criteria. Spousal interview data were obtained for 34 of these cases and 80 controls; interviews were refused by the remainder. Although matching of cases and controls was initially carried out, it was not retained in the analysis, and no demographic comparison of cases and controls used in the analyses is provided. Diagnoses were apparently drawn from patients' charts, provisional diagnoses were used where no final diagnosis was specified, no data on diagnostic technique(s) or histology is presented, and no diagnostic verification is reported.

The patient population consists of never-smokers, defined as lifelong nonsmokers, which presumably excludes cigar and pipe smokers. Exposure to ETS is approached in several ways. The primary exposure is that of a spouse smoking manufactured cigarettes at some point over the course of a marriage. Spousal smoking in the 12 months before interview was also assessed. In addition, "regular" exposure to passive smoke in various situations (i.e., at home or work, during travel or leisure) was assessed. The first two exposures were quantified in numbers of cigarettes smoked per day, the others in terms of "not at all, a little, average, or a lot." Thus, it appears that cigar and pipe smoking may not have been included in the spousal smoking exposures. Comparison of individual responses regarding spousal smoking status by patients and their spouses revealed a high degree of concordance (97%) for smoking during the last 12 months and a substantial concordance (85%) for smoking during marriage. No other checks on exposure data were reported.

The ETS patient data set includes 56 cases and 112 controls who met the initial study criteria. Not all of these answered each passive exposure question, however, and not all met the criteria for the spousal interview study. Similarly, spouses of 34 cases and 80 controls provided exposure information of varying completeness. Thus the numbers involved in each analysis varied considerably. For smoking during marriage, data obtained directly from spouses indicated that for males and females combined, 24 of 34 lung cancer cases and 51 of 80 controls were exposed, which yields a crude odds ratio of 1.4 for spousal smoking. With standardization for age, an odds ratio of 1.33 (95% C.I. = 0.50-3.48) was reported. Data obtained from qualifying patients, in contrast, revealed 13 of 29 cases and 27 of 59 controls to be exposed, yielding a crude *and* adjusted odds ratio of 1.00 (95% C.I. = 0.41-2.44). Stratification by gender yielded adjusted odds ratios from spousal interview data of 1.60 (0.44-5.78) and 1.01 (0.23-4.41) for females and males, respectively, with corresponding odds ratios from patient interview data of 0.75 (0.24-2.40) and 1.5 (0.37-6.34). When spouses identified as smokers by interview with either source were classified as exposed, an odds ratio of 1.00 (0.37-2.71) was obtained for female subjects. For the larger inpatient passive smoking study population, age-standardized odds ratios for passive smoke

250103221 3

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

exposure at home, at work, during travel, and during leisure revealed no consistent associations, with as many negative as positive relationships observed after adjustment for both age and whether still currently married. The same inconsistency held true for spousal smoking during the last 12 months and during the whole marriage. Adjustment for working in a dusty job reportedly did not affect the conclusion that passive smoking was not associated with risk.

Spousal smoking was slightly negatively associated with chronic bronchitis, ischemic heart disease, and stroke, whereas a combined ETS exposure index was negatively associated with heart disease but positively associated with bronchitis and stroke.

The author concluded that the findings appear consistent with the general view, based on all the available evidence, that any effect of passive smoking on risk of lung cancer or other smoking-associated diseases is at most quite small, if it exists at all. The marked increases in risk noted in some studies are more likely to be a result of bias in the study design than of a true effect of passive smoking.

A.24.3. Comments

The heart of this study is the spousal interview investigation of lung cancer and spousal smoking. Only 34 case spouses and 80 control spouses, and even fewer of the corresponding cases and controls themselves, are included, which gives the study low statistical power. Because the study began with hospital inpatient married lifelong nonsmokers, and matching on several key factors was employed, good comparability of cases and controls would seem readily achievable. No case-control demographics are provided, however, and matching is abandoned in the analyses. Undoubtedly, the high rate of refusals and frequency of omitted responses (themselves a potential source of selection and information bias) contributed to the decision to abandon matching, with the aim of preventing further substantial reduction in numbers through exclusion of unmatched subjects. The unfortunate result is that the comparability of the cases and controls is uncertain. At least all are drawn from the same four hospital areas within a fairly limited timespan, which, in combination with the other study criteria, reduces the likelihood of serious noncomparability.

Numerous opportunities for misclassification of disease and exposure status are present. Current working diagnoses are apparently drawn from patient charts without verification, and controls are selected from patients with diagnoses judged either probably or definitely not associated with smoking by unspecified criteria. This creates considerable potential for misclassification, both through inaccuracies in diagnoses generally and through inclusion of smoking-related diseases in the control group particularly, which would produce a downward bias in results. Exposure misreporting and recall problems would seem least likely where spouses are

2501032214

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

interviewed directly about exposure within the last 12 months. Results for this situation are not presented, although they are reportedly similar to those for smoking during marriage.

The larger inpatient study elicited smoking data from patients, and only for their *first* spouse for patients who had remarried; thus, exposure occurring in subsequent marriages is not addressed. In addition, no information on duration or level of smoking in marriage is used in any of the spousal smoking analyses. The most likely result of these problems is nondifferential misclassification resulting in a bias toward the null. For general estimated home, work, travel, or leisure exposure to passive smoke, rough quantification *is* attempted by having patients categorize their exposure as "not at all, a little, average, or a lot." By necessity, this is a very subjective evaluation, and people more acclimated to smoke and tolerant of exposure might well tend to characterize a given amount of exposure as less severe than would a person of less tolerance who more actively avoids exposure. This tendency would produce a bias toward negative association.

Standardization for age and restriction of cases and controls to currently married lifelong nonsmokers should control potential confounding by age, marital status, or active smoking, although misreporting of current or former active smoking cannot be ruled out entirely. Dusty occupation reportedly had no effect on the larger inpatient study results. Potential confounding by race, socioeconomic status, diet, cooking habits, or any additional factors was not addressed.

One might expect the most accurate reporting of spousal smoke exposure when spouses are interviewed directly regarding their own smoking habits, and the most inadvertent misclassification when patients are queried about the smoking status of their first marital partner only. Analyses along these lines yielded slightly positive associations with smoking for the former and negative with the latter approach. No consistent pattern of association was seen for other sources and lung cancer, although high combined exposure scores were associated positively with chronic bronchitis and stroke and negatively with ischemic heart disease.

In summary, this study presents equivocal results that neither strongly confirm nor refute the hypothesis that passive smoking mildly increases risk of lung cancer. The quality of the study, however, is a limitation. The discrepant results for subject-supplied data (OR = 0.75) and spouse-supplied data (OR = 1.60), varying degrees of completeness of information on subjects, the subjective nature of questions regarding ETS exposure, and lack of information on intensity or duration of husband's smoking do little to inspire confidence in the study's data and, consequently, the results from analysis of those data.

2501032215

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.25. LIU

A.25.1. Author's Abstract

"In Xuanwei County, Yunnan Province, lung cancer mortality rates are among the highest in China in both males and females. Previous studies have shown a strong association of lung cancer mortality with indoor air pollution from 'smoky' coal combustion. In the present case-control study, 110 newly-diagnosed lung cancer patients and 426 controls were matched with respect to age, sex, occupation (all subjects were farmers), and village of residence (which provided matching with respect to fuel use). This design allowed assessment of known and suspected lung cancer risk factors other than those mentioned above. Data from males and females were analyzed by conditional logistic regression. In females who do not smoke, the presence of lung cancer was statistically significantly associated with chronic bronchitis (odds ratio [OR] = 7.37, 95% confidence interval [CI]: 2.40-22.66) and family history of lung cancer (OR 4.18, 95% CI: 1.61-10.85). Females' results also suggested an association of lung cancer with duration of cooking food (OR 1.00, 9.18 and 14.70), but not with passive smoking (OR 0.77, 95% CI: 0.30-1.96). In males, lung cancer was significantly associated with chronic bronchitis (OR 7.32, 95% CI: 2.86-20.18), family history of lung cancer (OR 3.78, 95% CI: 1.70-8.42), and personal history of cooking food (OR 3.36, 95% CI: 1.27-8.88). In males a dose-response relationship of lung cancer with smoking index (years of smoking/amount of smoking) was shown by risks of 1.00, 2.61, 2.17 and 4.70."

A.25.2. Study Description

This study was undertaken in Xuanwei county of China's Yunnan Province, a county whose lung cancer mortality rates are among the country's highest and wherein burning of smoky coal indoors in unventilated pits is a common practice. The study sought to assess "the influence of factors other than type of fuel on the occurrence of lung cancer in Xuanwei."

Cases of newly diagnosed lung cancer occurring among farmers at hospitals and clinics in Xuanwei between November 1985 and December 1986 were identified as potential study subjects. Up to five controls were identified for each case, depending on availability after matching on age (± 2 years), gender, and village of residence. A total of 112 cases were identified, from which 2 were excluded due to unknown addresses. Of 452 candidate controls, 26 were excluded due to erroneous questionnaire responses. All subjects were interviewed face-to-face by trained personnel using a standardized questionnaire, and blinding extended to both interviewers and interviewees.

25010322 16

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The final study groups consist of 54 (56) female (male) cases and 202 (224) female (male) controls. Mean age is 52 years for both cases and controls, who are also similar in family size, ethnicity, birthplace, dwelling type, and type of fuel used (smoky coal, wood). Separate breakdowns for males and females are not provided. Very few of the cases (19/110 = 17%) were histologically or cytologically diagnosed, and no verification of diagnosis or exclusion of secondary tumors was undertaken (except to monitor mortality among some of the cases).

Exposure to ETS was not evaluated for males. Among females, only one subject (a control) reported ever having smoked, so the ETS population of females effectively consists of never-smokers. Subjects were classified as exposed to ETS if their household contained at least one smoker. Exposure is not quantified, and it is unclear whether former or only current exposure is intended. No checks on exposure status or consideration of marital status are mentioned, and no histological data are presented.

The ratio of exposed to unexposed female subjects is 45 out of 94 (176/202) for cases (controls), yielding a crude odds ratio of 0.74. A conditional logistic regression analysis adjusted for other risk factors (presumably the other factors referred to are age-began-cooking and years-of-cooking) gives an odds ratio of 0.77 (95% C.I. = 0.30-1.96). No further analyses of ETS exposure are provided.

Four non-ETS factors are significantly associated with lung cancer among females: family history of lung cancer (OR = 4.18; 95% C.I. = 1.61-10.85), personal history of bronchitis (OR = 7.37; C.I. = 2.40-22.66), age-began-cooking (OR = 2.44-1.03, but with a reversing and nonsignificant dose-response), and years-of-cooking (OR = 2.49-2.25, nonsignificant trend). Among males, significant positive associations were noted for total smoking index, often-cooking-own-food, family history of lung cancer, and history of chronic bronchitis, whereas age-began-smoking, years of smoking, and intensity of smoking showed modest but nonsignificant associations with lung cancer.

The authors conclude that "it is quite conceivable that the large amount of air pollutants inhaled during indoor smoky coal burning in Xuanwei partly overwhelm the carcinogenic effect of tobacco smoking" and "may also overwhelm the carcinogenic effect of passive smoking." "Our results disclose important associations of lung cancer with factors other than fuel type and therefore indicate that those factors must be considered in any comprehensive, quantitative risk assessment of lung cancer in Xuanwei. Our results also confirm indirectly that smoky coal pollution is an important determinant of lung cancer in Xuanwei."

2501032217

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.25.3. Comments

This modestly sized study was not designed to test for effects of ETS exposure. Rather, it is an hypothesis-generating exercise aimed at covering a broad range of possible risk factors. Within that context, the study has considerable merit, but as an investigation of ETS it has numerous flaws.

Restriction to farmers minimizes concerns with occupation and overall lifestyle, and control selection, including matching on age, gender, and village, produced demographically comparable case and control populations for males and females combined despite the enigmatic exclusion criterion for controls. It is unknown, however, whether the groups remain comparable after subdivision into males and females.

The use of newly diagnosed cases reduces potential selection bias due to inclusion of prevalent cases, but the heavy reliance (83%) on clinical and radiological diagnosis and the absence of independent confirmation or exclusion of secondary tumors introduces a strong potential for misclassification of disease and precludes analyses by cell type. The observation that follow-up of a number of lung cancer patients revealed that almost all died within 6 months of diagnosis does little to confirm diagnostic validity, contrary to the authors' interpretation. Such presumably random misclassification would make detection of an existing ETS-lung cancer association more difficult.

Exposure data collection procedures, particularly the exclusive use of face-to-face interviews without resort to proxies and the blinding of both interviewers and subjects, are laudable. For ETS, however, the exposure measure used is nonspecific and nonquantitative. Complications due to past exposure and differences in degree or duration could distort the observed disease-exposure relationship, probably biasing results toward no effect.

Potential confounding is not adequately addressed in the statistical analysis. The authors are particularly concerned with indoor smoky coal burning due to the known strong correlation between smoky coal use and lung cancer mortality in Xuanwei. Wishing to focus their investigations on factors other than smoky coal, they matched cases and controls on village, which "provided effective matching on fuel type." But because age and a host of other demographic factors, as well as smoky coal consumption, were comparably distributed in cases and controls (see Study Description), these factors were not considered further in the data analysis. This is a serious flaw, for pair matching was not retained in the analysis; thus, none of the above factors is effectively controlled for. The conditional regression analyses do control for risk factors other than those cited above, but exclusion of age, fuel type (e.g., smoky coal), and degree of exposure to fuel fumes may produce misleading results.

250103218

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

The presence of other significant risk factors for lung cancer makes detection of an effect from ETS, if present, less likely. Masking by the presence of smoky coal and other factors in the study environment is probably a factor in the remarkably weak association between active smoking and lung cancer among study males (adjusted OR = 1.36). If even an effect of active smoking remains largely obscured under study conditions, it is unlikely that an effect of ETS would be detected.

Overall, this study makes important contributions to its principal objectives but is not helpful in assessing ETS and lung cancer. It is observed, for example, that persons in areas of Xuanwei with high lung cancer rates (and high smoky coal consumption) may inhale more BAP (benzo-[a]-pyrene) by spending 8 hours indoors than by smoking 20 cigarettes. Due to such factors, the authors observe, "the effect of passive smoking on lung cancer may depend on local environmental factors and results obtained in a given region may therefore not be applicable to other regions." Avoidance of areas atypically rich in competing exposures and careful control of potential confounders and interactive risk factors must be key objectives in studies of ETS and lung cancer.

A.26. PERS

A.26.1. Author's Abstract

"The relation between passive smoking and lung cancer was examined by means of a case-control study in a cohort of 27,409 nonsmoking Swedish women identified from questionnaires mailed in 1961 and 1963. A total of 77 cases of primary carcinoma of the bronchus or lung were found in a follow-up of the cohort through 1980. A new questionnaire in 1984 provided information on smoking by study subjects and their spouses as well as on potential confounding factors. The study revealed a relative risk of 3.3, constituting a statistically significant increase ($p < 0.05$) for squamous cell and small cell carcinomas in women married to smokers and a positive dose-response relation. No consistent effect could be seen for other histologic types, indicating that passive smoking is related primarily to those forms of lung cancer which slow the highest relative risks in smokers."

A.26.2. Study Description

This case-control study, undertaken to explore the role of passive smoking in lung cancer, is based on cohorts of Swedish women assembled prior to 1963. Nonsmokers were drawn from these cohorts to create matched case and control groups.

250103219

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Cases are nonsmoking Swedish women included in the Swedish National Census or Twin Registry who responded to smoking status questionnaires in 1961-63 and who subsequently developed primary lung or bronchial cancer by 1980. Two control groups were cumulatively sampled from National Census or Twin Registry subjects who did not develop lung or bronchial cancer. In group 1, two controls were matched to each case on year of birth (± 1 year). In group 2, two controls were matched to each case (2:1) on year of birth (± 1 year) and vital status in 1980. Thus, there were 58 cases and 232 controls from the National Census and 34 cases and 136 controls from the Twin Registry. A follow-up questionnaire that included questions on spousal and parental smoking habits was distributed to each subject or the next-of-kin in 1984. Out of 92 cases of tracheal, bronchial, lung, or pleural cancer occurring by 1980, 15 cases in which a diagnosis of primary cancer of the lung or bronchus was not established were excluded. Exclusion of women indicated to be active smokers according to the 1984 questionnaire, or for whom ETS exposure information was not available, eliminated a further 10 cases. Active smoking and lack of exposure information eliminated 21 of the 368 controls initially assembled. Histological confirmation was available for 64 of the 77 cases with primary lung or bronchial cancer; 12 cases were cytologically confirmed; and the remaining case was verified at autopsy.

Never-smokers are subjects who report that they have never smoked any form of tobacco. A woman is ETS-exposed if she has ever been married to a tobacco smoker; for women married more than once, only the longest marriage is considered. Exposure to spousal smoking is quantified in units of cigarettes per day or packs of pipe tobacco per week; parental smoke exposure is defined as 0, 1, 2, etc. (equal to the number of parents who smoke). No other sources of ETS exposure are considered. Never-smoking status was checked by comparing the responses to the 1961-63 questionnaires with those obtained in 1984. Data on sources of ETS were not checked. Never-married women were classified as nonexposed to spousal smoke; widows and divorcees were classified according to the smoking status of the former husband with whom they had lived the longest. Of the never-smoking cases for whom passive smoking information was available, squamous and small cell tumors constituted 20 cases, 13 of whom were exposed to spousal smoke; of the other 47 cases, 20 were exposed to spousal smoke.

Responses to the ETS questionnaire were available for a total of 81 never-smoking cases and 347 never-smoking controls. The 67 cases with primary lung or bronchial cancer constitute the ETS study subjects. It is not clear how many of the 347 potential controls were employed in each analysis. Presumably many (up to 4 for each excluded case from the original 81 never-smoking cases) were not used in the matched analysis, whereas most or all were used in the unmatched analyses described subsequently.

05/15/92
250103220

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A total of 33 of the 67 cases were exposed to spousal smoking. Among the never-smoking women, matched analyses indicate that the odds ratio for marriage to a smoker is 3.8 (95% C.I. = 1.1-16.9) for squamous or small cell cancer compared to control group 1, 3.4 (0.8-20.1) compared to control group 2, and 3.3 (1.1-11.4) compared to both groups combined. For other cell types, corresponding odds ratios are 0.7, 0.8, and 0.8, respectively. Subsequent analyses abandoned matching and pooled all controls. For squamous and small cell cancer, high exposure to spousal smoking (15 or more cig./day or at least one pack of pipe tobacco/week for 30+ years) is associated with an age-adjusted odds ratio of 6.4 (1.1-34.7), whereas the lower exposure is associated with an odds ratio of 1.8 (0.6-5.3). The estimated odds ratios for other types of cancer are also elevated for the higher exposure, but not at the lower one. Odds ratios adjusted for age and spousal smoking when at least one parent smokes as well are above 1 (1.9; 95% C.I. = 0.5-6.2) for squamous and small cell types but not for other types.

Logistic regression analyses reportedly produced the same results as did the stratified analyses. In addition, occupation, household radon, and urban or rural status had no significant effect. It is notable, however, that for all cancers combined, the odds ratio for radon exposure is 1.4 (0.4-5.4), the odds ratio for spousal smoking is 1.2 (0.6-2.6), and the odds ratio for radon and spousal smoking combined is 2.5 (0.8-8.5). No separate analyses for squamous and small cell cancer are provided for radon and other potential confounders. The authors conclude that exposure to ETS is related primarily to the forms of lung cancer that show the highest relative risks in smokers. The results are internally consistent.

A.26.3. Comments

Although based on cohorts assembled for other purposes, this case-control study was specifically designed to investigate passive smoke exposure. Thus, all participants are ETS subjects, which are matched. Matching criteria are rather modest—birthdate (± 1 year) for control group 1 and birthdate and vital status for control group 2. Because the study targeted *all* cases detected in the same cohorts from which matching controls were randomly drawn, good comparability of cases and controls is likely. No demographic comparisons of cases and controls for whom ETS information was available—and thus who constituted the analytical subjects—were provided to confirm this, however. Data on active smoking among subjects were collected both at the start and after the end of mortality monitoring, providing an opportunity to verify the nonsmoking status over time and exclude individuals whose status had changed (apparently those reported in 1984 to have smoked daily for at least 2 years were so excluded). Thus, the probability of significant misclassification of active smoking status is low. Data on passive

2501032221

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

smoking were collected only after the end of mortality monitoring and by necessity employed proxy respondents extensively, so some misclassification of exposure is likely. Self-administration of questionnaires eliminates interviewer bias as a source of error, making misclassification less likely to be systematic, but preferential recall of smoke exposure by relatives of cancer victims could have produced a bias. Misclassification of disease is unlikely to have been a problem because most cases were histologically diagnosed and secondary lung cancers were excluded.

Consideration of spousal smoke exposure only in their longest marriage among women married more than once means that some of the unexposed group probably had substantial exposure to spousal smoking, creating a bias toward no association. Classification of all never-married women as unexposed despite possible smoking by cohabitants creates the same bias. Few subjects (less than 20%) were single, but the frequency of remarriage is unknown; therefore, it is unclear how important this bias might have been. Lack of consideration of workplace smoke exposure may also have contributed a bias toward the null hypothesis of no association.

The authors addressed a number of potential confounders. Restriction of subjects to women eliminates potential confounding by gender, and age is addressed by retaining age-matching or, alternatively, adjusting for age in all analyses. Reportedly neither occupation, radon, nor urban residence had significant confounding effects, which makes confounding by other factors related to socioeconomic status or lifestyle unlikely, too. An analyses of parental smoking controlled for spousal smoking. The authors do, however, present evidence that the odds ratio for simultaneous exposure to radon and spousal smoke approximately equals the sum of the separate odds ratios for radon and spousal smoke, consistent with additivity of the effects. But, perhaps due to limited numbers, they report results only for all cancers combined rather than for the squamous and small cell subgroup in which the only *significant* spousal smoking association was observed.

In summary, this study reports a consistent, dose-related, and (for high exposure levels) statistically significant positive association between exposure to spousal tobacco smoke and squamous and small cell carcinoma of the lung; a positive but nonsignificant association was also observed for parental smoke exposure. No significant associations were observed for other cell types. The observed associations apparently are not due to confounding by other major risk factors, although dietary and smoking habits were not directly addressed. A possible recall bias cannot be ruled out but seems unlikely given the negative results obtained for cancers other than squamous and small cell. The study provides a useful contribution to investigation of the relationship between ETS exposure and lung cancer.

2501032222

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.27. SHIM

A.27.1. Author's Abstract

"A case-control study of Japanese women in Nagoya was conducted to investigate the significance of passive smoking and other factors in relation to the etiology of female lung cancer. A total of 90 nonsmoking patients with primary lung cancer and their age- and hospital-matched female controls were asked to fill in a questionnaire in the hospital. Elevated relative risk (RR) of lung cancer was observed for passive smoking from mother (RR=4.0; $p<0.05$) and from husband's father (RR=3.2; $p<0.05$). No association was observed between the risk of lung cancer and smoking of husband or passive smoke exposure at work. Occupational exposure to iron or other metals also showed high risk (RR=4.8; $p<0.05$). No appreciable differences in food intakes were observed between cases and controls."

A.27.2. Study Description

This study was undertaken in Nagoya, Japan, during 1982-85 to investigate the significance of passive smoking and other factors such as occupational history, domestic heating system, and dietary habits in the etiology of lung cancer in nonsmoking Japanese women. All data were collected specifically for this study, which was limited to never-smokers.

All subjects were obtained from four hospitals in Nagoya. Cases are women with primary lung cancer (of any type) treated in these hospitals between August 1982 and July 1985 who reported themselves to be never-smokers and consented to interview. Controls are women with a diagnosis other than lung cancer from the same or adjacent wards with controls matched 2:1 with cases on age (± 1 year), hospital, and date of admission. Cases were not restricted to incident disease, but controls were essentially density-sampled by admission date. Data collection was by self-administered questionnaire; no attempt at blinding is described. Of 118 female lung cancer cases treated during the study period, four refused to participate in the study and 24 were excluded as current or former smokers. Only a single matching control could be found for 17 of the cases. No other information on loss of potential controls is provided. There is a total of 90 (163) cases (controls), with 52 (91) currently married to a smoker. Cases and controls share identical age ranges (35-81 years) and have nearly identical mean ages (59 years for cases, 58 for controls). All cases were histologically diagnosed, excluding secondary lung cancers.

All study subjects are self-reported never-smokers. A number of individual sources of ETS in the home are considered, including smoking by mother, father, husband, father-in-law, mother-in-law, offspring, and siblings. For each of these sources, smoking in the home at any time constituted exposure. Workplace exposure was characterized simply as presence or absence;

250103223

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

for other exposures, the number of cigarettes per day was obtained. In addition, data on length of marriage, time spent in the same room as the wife, and total number of cigarettes smoked were obtained for husbands. Exposure data were not checked, and marital status was not considered in the design or analysis of the study. The predominant type of lung cancer is adenocarcinoma (69 out of 90 cases), followed by squamous (13), large cell (4), small cell (3), and adenoid cystic carcinoma (1). No data on airway proximity are provided.

Logistic regression was used to estimate the relative risk for each source of ETS exposure. No significant association with lung cancer was noted for smoking by the husband (RR = 1.1), father (RR = 1.1), husband's mother (RR = 0.8), offspring (RR = 0.8), or siblings (RR = 0.8); smoking by the subject's mother (RR = 4.0) and by the husband's father (RR = 3.2), however, are significant ($p < 0.05$). None of eight dietary factors, including green-yellow vegetable and fruit intake, demonstrated a significant association, nor did type of cooking fuel or frequency of cooking oil use. Occupational history of exposure to iron or other metals shows a moderately strong but nonsignificant association (RR = 2.8), whereas for use of kerosene, coal, or charcoal heating there is a mild association (RR = 1.6-1.7).

Simultaneous stratification by father-in-law's and mother's smoking indicates that the effects of the two exposures are not additive. Smoking by father-in-law, smoking by mother, and occupational metal exposure were included simultaneously in a logistic regression model. After adjusting the effect of each variable for the other two, the relative risk for maternal smoking, father-in-law's smoking, and metal exposure are 2.1, 3.2 ($p < 0.05$), and 2.4, respectively. The authors conclude that the exposure to tobacco smoke from household members (i.e., mother or husband's father) could be associated with female lung cancer. As the precise situation of passive smoking in the home or other places is still unclear, however, they find that further studies are needed to clarify the significance of passive smoking in relation to the etiology of lung cancer in Japanese women.

A.27.3. Comments

This study employs a moderate number of well-matched cases and controls. Their comparability appears good, as supported by the identical age ranges and similar mean age and occupational categories for the two groups. A further strength of the study is its lack of reliance on proxy information with attendant potential for inaccurate recall. Exposure information was obtained from self-administered questionnaires, which eliminates the possibility of interviewer bias but may lead to inaccuracy due to misinterpretation of questions or varying care in their completion. Such problems with exposure information would tend to mask any actual association.

250103224

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Lung cancer was histologically diagnosed in all subjects and secondary lung cancers excluded, so diagnostic accuracy appears good for cases. Control diagnoses, however, were not validated, so some smoking-related disorders (in addition to the heart conditions noted in 3% of controls) may be included among the controls, a problem that once again would tend to reduce any observed association.

Restriction of subjects to never-smokers maximizes efficiency because effects of passive smoking would likely be dwarfed by active smoking. But it is unclear precisely what subjects were asked about their smoking status. Were any cut-points regarding pack-years or cigarettes per day specified? Was former smoking specifically questioned? Thus, some misclassification of smoking status may have occurred, and if a greater proportion of persons with smoking family members misreport themselves to be never-smokers, this would create an upward bias.

The authors restrict their assessment of exposure from relatives to at-home smoking, which may be more meaningful than total smoking as a potential source of passive smoke exposure. Furthermore, they collected data on smoking habits of all relatives, not just spouses or parents, thus reducing the chance of missing an exposure source. On the other hand, there is no consideration of total household smoking (all sources combined), cumulative exposure (except for husbands), or of pipe or cigar smoking; nor is there differentiation of current and former exposure--all potential sources of exposure misclassification, which would tend to make an association more difficult to detect.

Of the several sources of ETS exposure at home, only the relative risks for smoking by the mother and by the father-in-law are suggestive, and both of these are significant ($p < 0.05$). When these sources are considered simultaneously, however, and the effect of each is adjusted for the other, smoking by the husband's father remains significant (RR = 3.2; $p < 0.05$) but the effect of mother's smoking is diminished (RR = 2.1) and is not statistically significant. The authors' emphasis on the significance of exposure in childhood from maternal smoking appears misplaced. Exposure from the father-in-law is, of course, in adulthood. There is no evidence of an effect from husband's smoking (RR = 1.1), however, and these exposure sources were considered simultaneously so that the effect of one could be adjusted for the other. The large number of comparisons (e.g., eight groupings of passive smoke exposure, alternative spousal exposure measures, and several occupational and eight dietary factors) increases the likelihood that an observed relative risk will appear to be significant by chance alone (the effect of multiple comparisons).

Another aspect of the statistical analysis worth noting is that, although cases and controls appear well matched on age, hospital, and hospital admission date, these factors and other

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

potential confounders are not included in an adjusted analyses of the data (aside from the example with three sources of exposure described above). Consequently, possible confounding cannot be ruled out, although the demographic similarities between cases and controls make severe confounding less likely.

In summary, this study presents some interesting results. It finds a strong (adjusted RR = 3.2) and statistically significant association between father-in-law's smoking at home and lung cancer and associations for maternal smoking and occupational metal exposure as well. The lack of association for any of the other sources of ETS examined could be due to problems with exposure assessment and control disease criteria. Equally, however, given the unclear treatment of matching factors in the analysis, and the number of variables explored, the few substantial associations noted might be due to chance, confounding, or both. Were potential confounders clearly treated in their analyses, this study would have made a stronger contribution. As it stands, the study's data are of moderate utility, providing the number of comparisons and limitations regarding bias are kept in mind.

A.28. SOBU

A.28.1. Author's Abstract

"A hospital-based case-control study among non-smoking women was conducted to clarify risk factors in non-smoking females in Japan. Cases consisted of 144 non-smoking female lung cancer patients, and these were compared to 713 non-smoking female controls. The odds ratios (95% confidence interval) for use of wood or straw as cooking fuels when subjects were 30 years old was estimated as 1.77 (1.08 to 2.91). For those whose household members, other than husbands, had smoked, the odds ratio was estimated as 1.50 (1.01 to 2.32). For those whose mothers had smoked, the odds ratio was estimated as 1.28 (0.71 to 2.31). Use of heating appliances did not show an elevated risk. Some points to be noted in this study of low-risk agents for lung cancer are discussed."

A.28.2. Study Description

This study was conducted in Osaka, Japan, to clarify risk factors for lung cancer in nonsmoking females in Japan. Of interest are the roles of both active and passive smoking and other indoor air pollutants, particularly smoke or fumes from sources of indoor cooking and heating. This article reports only on female nonsmokers in the study, which is not matched on any variables. A very similar article presenting interim results and using slightly fewer subjects than the one described here is by Sobue and coworkers (1990).

250103226

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Cases consist of all newly admitted lung cancer patients in eight Osaka hospitals between January 1986 and December 1988. Controls were collected from newly admitted patients in one or two other wards of the same hospitals during that period. Almost 90% of the controls were admitted as cancer patients, about half of which were diagnosed with breast cancer. Self-administered questionnaires designed for this study were completed by both cases and controls at the time of hospital admission. Cases are incident and control sampling is density, unmatched aside from the time of hospital admission (within 1.5 years). The entire study, including active smokers and males, consists of 295 (1,079) female (male) cases and 1,073 (1,369) female (male) controls. Nonsmoking females compose 156 cases, of which there was missing information on 12. The resultant number of ETS subjects is 144 (731) female nonsmoking cases (controls). The age distribution of the cases (controls) is as follows: 40 to 49, 20 (238); 50 to 59, 34 (229); 60 to 69, 41 (186); and 70 to 79, 34 (78). The corresponding percentages are 14 (33), 34 (31), 28 (25), and 24 (11), which indicates that controls tend to be younger than cases. Also, the mean age of cases (controls) is 60 (56). There was no systematic review of histological diagnosis. All original diagnoses were confirmed microscopically, however, and all the pathologists involved in the eight participating hospitals were experienced specialists in lung cancer. Thus, the likelihood of secondary lung cancers among the cases should be small.

Several sources of ETS exposure are included, all of which occur in the home. Exposure in adulthood is expressed by two measures--smoking by the husband and by other household members (the last category consists chiefly of households where the husband's father and/or sons smoke). Three sources of exposure in childhood are considered--father smokes, mother smokes, and other household members smoke. No information is provided on how exposure to spousal smoking is handled for unmarried women (single, divorced, or separated). The entire complement of cases and controls is included in the summary data for each of the five sources of exposure given above. If only married women were included in the study, no mention of it was found.

The histological data for ETS subjects are not classified by exposure to ETS, but the percentage of cases by cell type are given: squamous cell (8), small cell (5), adenocarcinoma (78), large cell (5), and other (4). The ETS data on spousal smoking consists of 80 out of 144 (exposed/total) cases and 395 out of 731 controls, for an odds ratio of 1.13 (95% C.I. = 0.78-1.63). (Our calculations give 1.06 [0.74-1.52].) The odds ratio for ETS exposure from other household members in adulthood is 1.57 (95% C.I. = 1.07-2.31). (Our calculated values are 1.77 [1.21-2.58].) For ETS exposure in childhood by the father, by the mother, and by other household members, the respective odds ratios are 0.79 (95% C.I. = 0.52-1.21), 1.33 (95% C.I. = 0.74-2.37), and 1.18 (95% C.I. = 0.76-1.84). Tests were conducted by the Mantel-Haenszel procedure, with

2501032227

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

stratification by age and education (two levels). Analysis by logistic regression, adjusted for age at time of hospitalization, was conducted for two of the exposure measures described above with similar outcomes. Based on this evidence, the author concludes that for childhood exposure, a slight increase of risk was suggested for those with smoking mothers, although statistical significance was not observed. For exposure in adulthood, an elevated risk was estimated for those with smoking household members other than husbands.

The statistical analysis includes exposure to sources other than ETS, namely, the use of wood or straw as cooking fuel, the use of heating equipment that pollutes the room with combustion products, and the use of charcoal foot warmers. All exposures considered, including ETS, are smoke or fumes from products burned indoors. It is concluded that significantly elevated risks were observed for subjects who had used wood or straw as cooking fuels at 30 years of age (OR = 1.89; 95% C.I. = 1.16-3.06). No elevated risks were found for sources of indoor heating (use of kerosene, gas, coal, charcoal, and wood stoves without chimneys). Similarly, no significance was found for the use of charcoal foot warmers, a practice that was popular until the 1960's.

A.28.3. Comments

With 144 cases and 731 controls, the sample size is larger than many of the other case-control studies on ETS. Information on cases and controls was obtained by self-administered questionnaire, which is generally considered less reliable than face-to-face interviews. The questionnaires were presumably completed by the subjects themselves in all cases, however, which is preferable to proxy-supplied information. The information supplied was not verified from other sources, as noted by the authors in reference to testing for biomarkers of exposure to tobacco smoke (they note that laboratory tests can only detect recent exposure, but they could still be useful in eliminating current smokers who may misreport themselves as never-smokers). Although cases and controls were newly diagnosed patients within a short time period in the eight participating hospitals and were supplied with the same questionnaire, there are still some questions regarding the comparability of cases and controls and their representativeness of the target population.

Controls tend to be younger than cases: Mean ages are 56 and 60, respectively, and 33% of controls, compared to 14% of cases, are below the age of 40. Controls also tend to be more educated than cases, with 69% of controls having completed 10 or more years of education compared to 52% of cases. Differences in age and educational level further reflect differences in lifestyle and socioeconomic status that may affect risk of disease. Also, the controls are

250103228

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

predominantly cancer patients too, almost half with breast cancer. Although the diseases of the controls may not be known to be related to tobacco use, controls may be a biased sample (as noted by the authors). Furthermore, the statistical analysis stratifies on age and education so, even though cases and controls were not strictly matched on these variables, the reported results should not be due to confounding by either of these factors. On the other hand, exclusion of breast cancer controls reportedly leaves the results unchanged.

Although some of the issues and reservations described above are methodological in nature and apply to the study throughout, others are specific to the ETS data alone. For example, one might expect a question regarding the use of cooking with wood or straw at age 15 and at age 30 to be open to little subjective interpretation or error in recall, presuming that methods of cooking persisted for several years between changes within a household. Although there is some suggestive evidence of increased lung cancer from ETS exposure (the reservations above set aside for the moment), the statistical evidence may be stronger for an association between lung cancer prevalence and use of wood or straw for cooking at age 30. Further support is provided by the observation that among those who had used wood or straw for cooking at age 30, 90% had also used those fuels at age 15, suggesting extended exposure in most cases. The age distribution of those exposed to wood or straw cooking is not given, but exposure at 30 years of age and before would allow for the long latency expected for lung cancer because 86% of the patients are at least 50 years of age.

The smoke from cooking sources may obscure or distort any impact of ETS exposure because the two sources probably contain some of the same carcinogens. The temporal dimension of exposure may also be a factor because indoor smoke from cooking may be less common at present than 30 years ago in comparison to ETS exposure. Further statistical analysis to adjust the effect of ETS exposure for the presence of smoke from cooking might aid interpretation of the results in this study, depending on the extent of confounding present.

A.29. STOC

A.29.1. Author's Abstract

(*Note:* This study has not been published. Only the abstract is available, which is given below.)

"Risk factors for lung cancer among women who had never smoked cigarettes were examined in an ongoing, population based, case-control study conducted in Florida. One hundred and twenty-four primary carcinomas of the lung, and 241 control women who had never smoked were included. Results suggest that childhood and adult exposures to environmental tobacco smoke may increase the risk of lung cancer among women who never smoked cigarettes. Having a

2501032229

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

husband who smoked cigarettes resulted in a statistically significant increase in risk of lung cancer among women who had never smoked, with an odds ratio of 1.8 (95% C.I. 1.1-2.9). A 40% increase in risk was observed among women with less than 25 years of exposure to a spouse who smoked, when compared to women who reported their spouse had never smoked, with the risk increasing to 60% among women exposed 25 years or longer.

When exposure to tobacco smoke in childhood was considered, the data were less consistent. Having a parent who had smoked during the respondent's childhood did not increase the risk of lung cancer. However, among those respondents with high levels of exposure to parental smoking, an excess risk, although not statistically significant, was observed. Never smoking women who accumulated 25 or more exposure years experience a 70% increase in risk (OR = 1.7, 95% C.I. 0.8-3.6) of lung cancer compared to women who reported neither parent had smoked cigarettes."

A.30. SVEN

A.30.1. Author's Abstract

"In a population based-case control study the association between female lung cancer and some possible etiological agents was investigated: 210 incident cases in Stockholm County, Sweden, and 209 age-matched population controls were interviewed about their exposure experiences according to a structured questionnaire. A strong association between smoking habits and lung cancer risk was found for all histological subgroups. Relative cancer risk was found for all histologic subgroups. Relative risk for those who had smoked daily during at least one year ranged between 3.1 for adenocarcinoma to 33.7 for small cell carcinoma in a comparison with never-smokers. All histological types showed strong dose-response relationships for average daily cigarette consumption, duration of smoking, and cumulative smoking. There was no consistent effect of parental smoking on the lung cancer risk in smokers. Only 38 cases had never been regular smokers and the risk estimates for exposure to environmental tobacco smoke were inconclusive. The high relative risks of small cell and squamous cell carcinoma associated with smoking may have relative implications for risk assessments regarding passive smoking."

A.30.2. Study Description

This study was undertaken in Stockholm County, Sweden, from 1983 to 1986 to investigate the association between female lung cancer and some possible etiologic agents, particularly active and passive smoking. Because active smoking was an exposure of interest, cases and controls were not matched on smoking status; thus, the ETS study population is unmatched.

2501032230

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Cases are Swedish-speaking women with primary lung cancer from three Stockholm County hospitals who were willing and able to be interviewed between September 1983 and December 1985. Cases with carcinoid tumors were excluded from the ETS analysis. Both population and hospital-based control groups were assembled. Population controls were women randomly selected from the county population register, matched to a case on birthdate and interviewed between September 1983 and December 1986. Hospital controls were subjects originally interviewed as potential lung cancer cases but subsequently diagnosed with nonmalignant conditions. Population controls were enlisted and interviewed as soon as a case's diagnosis was confirmed, but because this confirmation took as long as a year after the interview, controls were not density sampled. Unblinded interviews were conducted face to face with all cases (and hospital controls) and 58% of the total population controls; the remainder were interviewed by telephone.

After exclusion of 21 potential cases due to initial diagnostic uncertainty, refusal, or illness precluding interview, 210 confirmed cases remained. Elimination of 172 ever-smokers and four subjects with carcinoid or not-microscopically-confirmed tumors left 34 never-smoking cases. Similarly, 209 population and 191 hospital controls were included in the total study, but a combined total of only 174 were never-smokers. The total case population averaged 62.5 years of age, but no other demographic information regarding cases or controls is provided. All cases used in the ETS analyses were histologically or cytologically confirmed primary lung cancers.

Daily smoking for at least 1 year is the criterion for a smoker; all other persons are considered never-smokers. Pipe and cigar smoking are never specifically addressed. Exposure to ETS is calculated for four sources: mother, father, home, and work. Having a smoking mother or father (at any time during ages 0-9 years) constitutes exposure to that particular source, whereas the presence of a smoker at home and work constitutes exposure. Adulthood and total lifetime exposure are considered separately for home and workplace exposure. Exposure levels are arbitrarily scored 1 for nonexposure, 2 for exposure to one source, and 3 for exposure to both sources in trend analyses of never-smokers, where exposures are considered in pairs (i.e., maternal and paternal smoking, home and workplace exposure). No other units of ETS exposure are used. Adenocarcinomas constituted 22, squamous cell 5, and small cell 2 of the 34 lung cancers occurring among never-smokers in the ETS population; no further histologic details regarding the ETS study population are provided.

To maximize available case numbers, parental smoking was first analyzed among all cases and community controls using stratification to adjust for active smoking (cig./day) and age. A risk of 1.8 (95% C.I. = 0.5-7.0) was estimated for maternal smoking and 0.8 (0.3-1.4) for paternal

250103223

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

smoking. A trend analysis in which maternal, paternal only, and no parental smoke exposure were scored as 3, 2, and 1, respectively, revealed no indication of trend ($p = 0.9$). Analyses restricted to never-smokers used both community *and* hospital-based controls combined. Among cases (controls), for childhood up through 9 years of age, 3 (5) had smoking mothers, 12 (71) had smoking fathers (but not mothers), and 19 (98) were unexposed. This yielded an age-adjusted risk estimate of 3.3 for maternal smoking (with or without paternal smoking) and 0.9 for paternal smoking during childhood. Adult exposure at home *and* at work yielded an estimated risk of 2.1, whereas exposure at home *or* work yielded a risk of 1.2. For lifetime exposure, the estimated risks for exposure as both a child *and* adult and as either a child *or* an adult were 1.9 and 1.4, respectively. None of these associations were statistically significant, and no significant trends were observed. The authors conclude that the results pertaining to ETS in the present study were not conclusive. The small number of never-smokers among the cases could be one important reason. It should be noted, however, that most of the point estimates of relative risk were greater than unity, which agree with results from previous studies on ETS exposure and with risk estimates concerning active smoking.

A.30.3. Comments

This study was undertaken to explore the role of active as well as passive smoking in lung cancer. After exclusion of active smokers, the available number of cases is too small to yield much statistical power.

Cases and population-based controls were initially matched on date of birth, but this matching was abandoned in the ETS analysis; furthermore, unmatched hospital-based controls are combined with the population-based controls in most analyses to boost available numbers. The comparability of these groups is thus unclear, and the authors provide no demographic comparisons to facilitate assessment of this potential problem. The reported similarity of results using only population-based controls is reassuring, but no details are provided as to *how* similar results actually were.

Diagnostic misclassification of cases is unlikely, given the histological or cytological confirmation of all cases and exclusion of secondary cancers. All cases were interviewed face to face, but 42% of controls were interviewed by telephone. The accuracy of responses may thus be lower for controls than for cases. And because interviews were not conducted blindly, inflation of estimated associations through interview bias is possible. A potential bias is also introduced by the rather large amount of active smoking required for classification as an ever-smoker. This allows considerable active smoking among persons in the never-smoker group, the effect of which could

2501032232

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

mask an effect of passive exposure, or, if covarying positively with passive smoking, cause overestimation of association.

The first set of analyses of paternal and maternal smoking includes ever-smokers while attempting to adjust for active smoking on the basis of average daily cigarette consumption. The adequacy of this adjustment is questionable given the large estimated risks associated with active smoking relative to those posited for passive smoking, so the elevated estimated risks for maternal smoking obtained in these analyses are of questionable validity.

Restriction of the analyses to never-smokers similarly produces an elevated odds ratio for maternal smoking of 3.3, but the numbers involved (three cases and five controls) are so small that this value is quite unstable. A pattern of increasing estimated risk with increasing sources of exposure (at home or at work) as an adult and increasing periods of exposure (in childhood or adulthood) over the lifetime is suggestive of an association between lung cancer and ETS, but again small numbers preclude statistical significance of these results.

Restriction of the study population to females rules out the possibility of confounding due to gender. The likelihood of an ethnicity effect is reduced by restriction to Swedish-speaking residents of Stockholm County, and age is reportedly controlled for in all analyses. No other potential confounders are addressed. For example, marital status is not considered in the analyses of spousal smoking, leaving open the possibility that nonsmoking-related differences between married and unmarried women contributed to the observed association. The reported similarity of results when only population controls were used instead of hospital and population controls combined provides a general argument against confounding, although no specifics regarding the degree of similarity were supplied.

In summary, this study presents consistent evidence of associations between lung cancer and maternal, home, and workplace passive smoking exposure. Limited numbers preclude statistical significance and interviewer bias or confounding due to dietary or other factors cannot be ruled out as contributors to the observed results. Bearing these limitations in mind, the study's results are inconclusive but (excluding the analyses that include active smokers) do make a useful contribution to the pool of information available regarding ETS and lung cancer.

A.31. TRIC

A.31.1. Author's Abstract

"Fifty-one women with lung cancer and 163 other hospital patients were interviewed regarding the smoking habits of themselves and their husbands. Forty of the lung cancer cases and 149 of the other patients were nonsmokers. Among the nonsmoking women there was a

250103223

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

statistically significant difference between the cancer cases and the other patients with respect to their husbands' smoking habits. Estimates of the relative risk of lung cancer associated with having a husband who smokes were 2.4 for a smoker of less than one pack and 3.4 for women whose husbands smoked more than one pack of cigarettes per day. The limitations of the data are examined; it is evident that further investigation of this issue is warranted."

A.31.2. Study Description

This study was undertaken in Athens, Greece, to investigate the relationship of spousal smoking and lung cancer. All female Caucasian Athenian residents admitted to one of three chest or cancer hospitals in Athens and assigned a final diagnosis of lung cancer other than adenocarcinoma and alveolar carcinoma from September 1978 through June 1980 were interviewed by a physician. Controls were gathered from nonsmoking female Caucasian Athenian patients hospitalized during the same time period in the Athens Orthopedic Hospital. Some prevalent cases were thus presumably included, so control sampling probably approximated a density approach but did not strictly conform to one.

Diagnostic information was obtained from patients' charts. Exposure information was obtained by face-to-face unblinded interviews conducted by the same physician for all subjects. A total of 51 cases and 163 controls were interviewed. Of these, 11 cases and 14 controls reported themselves to be active smokers, leaving 40 cases and 149 controls as ETS subjects. No interview refusals are reported. Mean age of cases (controls) is 62.8 (62.3) years. Husband's education was marginally higher in controls than cases with 63% and 58% of spouses having completed primary school, respectively. No other demographic comparisons are reported for the ETS subjects alone. For the sample population including smokers, factors such as age, duration of marriage, occupation, education, and urban versus rural residence are all similar for cases and controls, except once again educational level is slightly higher for controls. There is no indication that verification of diagnosis or exclusion of secondary lung cancers was undertaken in cases. Of the 51 total cases, 14 were diagnosed histologically, 19 cytologically, and 18 by radiological or clinical means. No breakdown is given for the ETS subjects alone.

The study classifies as nonsmokers both reported never-smokers *and* former smokers who quit more than 20 years ago. It is not mentioned whether cigar and pipe smoking are considered as sources of exposure. Nonsmoking women are considered exposed to ETS if they are married to a man classified as a smoker. The average number of cigarettes smoked per day by the husband and the number of years of marriage are used to estimate the total number of cigarettes smoked by the husband during marriage. No data on childhood or nonspousal ETS exposure were collected.

25010322 34

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Single women are grouped with women married to a nonsmoker and are thus considered unexposed. Widowed or divorced women were classified according to their former husband's smoking status on the assumption that smoking stopped at death or divorce. No checks of exposure information are reported.

For ETS subjects, the number of cases (controls) exposed over the total is 29 to 40 (78/149). The crude odds ratio calculated by the reviewers is 2.4 (95% C.I. = 1.12-5.16). The results presented in the article are all stratified by level of husband's smoking. The odds ratios are 1.8, 2.4, and 3.4 when the husband is a former smoker, smokes 1 to 20 cigarettes per day, and smokes 20 or more cigarettes per day, respectively. No confidence intervals are given, but a test for upward trend was statistically significant ($p < 0.02$). When ETS exposure is estimated by total number of cigarettes smoked during marriage, odds ratios (1.3, 2.5, and 3.0) increase with cumulative exposure (1-99, 100-299, and 300+ thousand, respectively). The upward trend remains statistically significant at $p < 0.02$. No analyses adjusted for age or other potentially confounding variables. With regard to age and other demographic variables, the authors conclude from the similarity of cases and controls that it is not necessary to stratify for these variables in the analysis, particularly because none is significantly associated with smoking in the study.

The authors note that this study has obvious limitations and is offered principally to suggest that further investigation of this issue should be pressed. Most seriously, the numbers of cases are small. Nevertheless, the association is in the direction expected if passive smoking is related to lung cancer, and the outcome is unlikely to be due to chance. Other limitations noted include the high percentage (35%) of cases lacking cytology and the selection of controls from a hospital different from those of the cases; it is argued, however, that neither of these appears to be consequential. The observation is made that it is potentially easier to detect an effect of passive smoking in the Greek population than in most Western populations, because in the latter groups, the overwhelming effects of active smoking, together with the high correlation between smoking habits of spouses, would tend to confound and conceal the lesser effects of passive smoking.

A.31.3. Addendum

In a letter to the editor of *Lancet* in 1983, Trichopoulos et al. released a data table derived from extension of subject collection through December 1982. This nearly doubled the sample size used in the 1981 publication, yielding 77 nonsmoking cases (102 total) and 225 smoking controls (251 total). The crude odds ratio calculated by the reviewers is 2.08 (95% C.I. = 1.20-3.59). The results for the expanded study show very little change; (estimated) relative risks when husbands

2501032235

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

are former smokers, (1-20 cig./day and > 20 cig./day) compared to nonsmokers are 1.95, 1.95, and 2.54, respectively. The test for upward trend in the dose-response is significant (p = 0.01). No other analyses are presented.

A.31.4. Comments

This study was conceived and undertaken to explore the association of spousal smoking with lung cancer and does not rely on a preexisting data set. Thus, the investigators were in a position to design their selection and data collection to maximize the strength of their findings. This did not, however, prevent the appearance of some design and analytical flaws.

Demographics of the total case and control populations are very similar. All subjects in the spousal smoking analysis are resident Athenian nonsmoking women hospitalized in the same area of Athens; case and control groups have very similar mean ages, and their husbands are comparable in education. Thus, the groups probably have good demographic comparability, although it would have been helpful if the detailed demographic comparisons were focused on the nonsmokers alone. Most of the controls (108 out of 163) were being treated for fractures, a relatively minor and nonchronic illness compared to lung cancer, which may make them more representative of the general community than of hospitalized patients as a whole. This should reduce the problem of inclusion of smoking-related illnesses in the control group.

Although the researchers sought to exclude adenocarcinomas and alveolar carcinomas, presumably considering these would be less smoking-related, nearly two-thirds of the cases were not histologically confirmed, so an indeterminate number of these cell types was probably included. More important, the infrequency of histologic confirmation and lack of mechanisms to verify diagnoses or primary tumor status introduces potential for misclassification. The likely effect is a bias toward no association.

The researchers clearly devoted considerable thought to the smoking and exposure criteria, particularly with regard to changes in smoking and marital status over time. Single women were, however, automatically classified as unexposed. The authors contend that this is warranted by the traditional nature of Greek society and report that analyses restricted to married women result in similar, and still statistically significant, associations, although with somewhat lower estimated risks. There is a small reduction in the odds ratios after exclusion of single women, however, and the restriction of the full analyses and results to married women may have been useful.

Another issue related to exposure concerns inclusion of former smokers in the study, provided they had not smoked for at least 20 years. Active smoking 20 to 30 years before the onset of lung cancer may be of etiological relevance, however, in view of a long latency period for

250103223

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

lung cancer. Although use of the same interviewing physician for all subjects eliminates the problem of interobserver variability, it magnifies the potential problem of interviewer bias in exposure assessment, presumably toward a positive association, because the interviews were apparently conducted unblinded (virtually unavoidable with regard to diagnosis, given that controls were drawn from orthopedic trauma and rheumatology wards).

A larger concern, however, is the issue of potential confounders. It is contended that the similar distribution of demographic variables between cases and controls eliminates the need to consider these variables in the analyses, but similarity between cases and controls does not preclude confounding from an independent risk factor differentially distributed by *exposure*. More convincing is the contention that these variables were not significantly associated with smoking in these data, although no specifics are included. Potential confounders such as diet, cooking, and heating practices are not addressed. The appearance of a statistically significant trend, for ETS exposure measured by either current spousal smoking or cumulative cigarette consumption during marriage, supports an association between spousal smoking and increased lung cancer incidence.

Overall, the issues addressed above would probably produce a conservative bias, resulting in an underestimate of the degree of association. The study's basic design is sound. It provides statistically significant evidence of dose-response, and although the limitations described above should be borne in mind, it provides useful data for assessment of the relationship between ETS and lung cancer.

A.32. WU

A.32.1. Author's Abstract

"A case-control study among white women in Los Angeles County was conducted to investigate the role of smoking and other factors in the etiology of lung cancer in women. A total of 149 patients with adenocarcinoma (ADC) and 71 patients with squamous cell carcinoma (SCC) of the lung and their age- and sex-matched controls were interviewed. Personal cigarette smoking accounted for almost all of SCC and about half of ADC in this study population. Among nonsmokers, slightly elevated relative risk(s) (RR) for ADC were observed for passive smoke exposure from spouse(s) [RR = 1.2; 95% confidence interval (CI) = 0.5, 3.3] and at work (RR = 1.3; 95% CI = 0.5, 3.3). Childhood pneumonia (RR = 2.7; 95% CI = 1.1, 6.7) and childhood exposure to coal burning (RR = 2.3; 95% CI = 1.0, 5.5) were additional risk factors for ADC. For both ADC and SCC, increased risks were associated with decreased intake of β-carotene foods but not for total preformed vitamin A foods and vitamin supplements."

2501032237

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.32.2. Study Description

This study was undertaken in California during 1981 and 1982 to investigate the role of smoking and other factors in the etiology of lung cancer in women. These other factors included prior lung disease, coal heating and cooking, diet, and occupation. Both active and passive smokers are included; some of the ETS analyses retain active smokers while attempting to adjust for smoking status.

Cases are white female English-speaking Los Angeles County residents under 76 years of age at time of diagnosis with primary adenocarcinoma or squamous cell cancer of the lung between April 1, 1981, and August 31, 1982. Cases are restricted to U.S.-, Canadian-, or European-born individuals with no history of prior cancer other than nonmelanoma skin cancer. Controls are density sampled, matched individually on neighborhood and age (± 5 years), and meet all case criteria (except, of course, diagnosis of lung cancer). The L.A. County tumor registry was used to identify incident cases for inclusion in the study, whereas controls were recruited house to house. Interviews to obtain exposure data were conducted by telephone with participating subjects, apparently unblinded.

A total of 490 eligible cases were identified; 270 were not interviewed because they were too ill or had died (190), their physician refused permission to contact them (28), they could not be located (8), or they refused (44). Those not interviewed did not differ significantly from those interviewed with regard to age or their marital, religious, or smoking status as recorded on registry records. Refusals eliminated 70 potential controls. The case and control populations had nearly identical mean ages for adenocarcinoma, 59.7 versus 59.5 years, respectively, and for squamous cell cancer, 61.4 versus 61.1 years. No other demographics are provided. Histologic diagnoses were obtained for all cases.

For spousal smoking, exposure constitutes having a spouse who smoked while living with the subject. For workplace smoke, exposure is based on the opinion of the subject. It is not clear whether for the lung cancer analyses, parental smoking refers only to adult life (as for spousal and workplace exposure) or to the childhood and teen years (as was stipulated for coal and preadult lung disease exposures). Adult life seems most probable. Units of exposure for spousal and parental smoking are cigarettes per day and years of exposure, apparently entered into a regression model as a combined variable; for occupational exposure, units are in years of exposure. Exposure data were apparently not checked, treatment of cigar and pipe smoking is never mentioned, and no results are reported for household smoking aside from spouse and parents, although information on this exposure was collected. Never-married women were excluded from the spousal smoking analysis, but marital status was not otherwise considered in the analyses. The

2501032238

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

only histologic or airway proximity information provided for the ETS subjects is that 29 adenocarcinomas occurred among nonsmokers, 12 of which were bronchoalveolar.

The total study population includes 220 cases and an equal number of matched controls. Of the cases, 149 are adenocarcinoma and 71 are squamous cell. Nonsmokers constituted 29 of the adenocarcinoma cases and 62 of the corresponding controls, while composing 2 of the squamous cell cases and 30 of the controls. No raw data are presented regarding passive smoking and lung cancer. Logistic regression analysis of matched pairs was used in all calculations. Results restricted to nonsmokers are presented only for adenocarcinoma. An estimated relative risk of 1.2 is found for spousal smoking, 1.3 for workplace exposure, and 0.6 for smoking by either parent. None of these estimates was statistically significant. Exposure from spouses and at work, however, show a dose-response trend with years of exposure, yielding estimated relative risks of 1., 1.2, and 2.0, for 0, 1 to 30, and 30 or more years of exposure, respectively.

Analyses that include active smokers but attempt to adjust for them by including the number of cigarettes smoked per day and age at start of smoking in a logistic regression model are presented for both lung cancer types. For adenocarcinoma, estimated relative risks for maternal, paternal, spousal, and workplace exposure of 1.7, 1.3, 1.2, and 1.2, respectively, were obtained. For squamous cell cancer, maternal, paternal, spousal, and workplace relative risks are 0.2, 0.9, 1.0, and 2.3, respectively. None of these estimates is statistically significant.

History of lung disease at least 5 years prior to diagnosis of lung cancer reportedly had no significant association with lung cancer. History of lung diseases before age 16 yielded a significant association for pneumonia (RR = 2.7 [95% C.I. = 1.1-6.7] for adenocarcinoma and RR = 2.9 [95% C.I. = 0.5-17.4] for squamous cell cancer) but not for six other diseases.

Heating or cooking with coal during the childhood and teenage years is also significantly associated with lung cancer (RR = 2.3 [95% C.I. = 1.0-5.5)] for adenocarcinoma and RR = 1.9 [95% C.I. = 0.5, 6.5] for squamous cell). Among dietary factors, low beta carotene consumption is significantly associated with adenocarcinoma (RR = 2.7) and mildly associated with squamous cell (RR = 1.5). Diets low in dairy products and eggs have similar relative risk values. No significant associations were noted for vitamin A consumption, occupation, or other health history factors not previously considered.

The authors conclude that the etiology of squamous cell carcinoma can be explained almost entirely by cigarette smoking. Cigarette smoking, however, explains only about half of the adenocarcinoma cases. On the basis of this study, childhood lung disease and exposure to coal fires in childhood explain at least another 22% of adenocarcinoma cases. Passive smoking and

250103239

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

vitamin A may be involved, but more research is needed to clarify their roles in lung cancer etiology.

A.32.3. Comments

This study took particular care with its treatment of case and control assembly. Extensive inclusion criteria extending to both groups, matching not only on age but neighborhood of residence, and retention of matching through analysis all bode well for comparability of cases and controls. The virtually identical mean ages of cases and controls indicate the success of these efforts. In addition, exclusive use of incident cases reduces the potential for selection bias, and density sampling of controls reduces potential problems with temporal variation. The only real fault in the treatment of cases and controls is the failure to provide any demographic comparison other than for age, thus denying concrete confirmation of high case-control comparability.

Case diagnoses are likely to be accurate, because all were histologically diagnosed, making misclassification unlikely and making cell-type-specific analyses possible. Although no one pathologist or team verified these determinations, the authors note that there is generally good interobserver agreement for the cell types included in this study. Potentially eligible cases not interviewed due to illness, refusal, or other reasons did not differ significantly in demographic or smoking status from those actually interviewed, again arguing against biased selection.

No proxy interviews were used and all subjects were English-speakers, enhancing the chances of obtaining accurate exposure information. On the other hand, interviews were by telephone—possibly decreasing accuracy relative to face-to-face interviewing--and apparently unblinded, thus introducing possible interviewer bias toward positive results.

Collection of exposure data seems generally adequate, except that treatment of pipe and cigar smokers is not described. Uncertainty on this point extends to the analysis and is coupled with a vague treatment of parental smoking (current only? childhood only? or both?) and lack of treatment of household smokers other than parents or spouses, despite collection of data on this point. These uncertainties probably translate into nondifferential exposure misclassification, biasing results toward the null.

The analyses themselves suffer from the common problem of restricted numbers of nonsmoking cases—29 for adenocarcinoma and only 2 for squamous cell. Some factors examined are restricted to nonsmokers alone for adenocarcinoma, but for most analyses, an adjustment for active smoking by logistic regression modeling was attempted. The adequacy of such adjustment may be questionable. For adenocarcinoma, however, the results for passive smoking were very similar, regardless of whether restriction or adjustment was used. Further, a dose-response

2501032240

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

pattern was seen for cumulative years of spousal and workplace exposure among nonsmokers. The utility of the smoking-adjusted cell analyses is nevertheless questionable, given the paucity of nonsmoking cases.

The findings of substantial associations between lung cancer (or, at least, adenocarcinoma) and childhood pneumonia and coal burning are of interest. It must be borne in mind that seven adult respiratory diseases (including pneumonia) as well as six other childhood respiratory diseases were examined, so the possibility that the pneumonia association was an artifact of multiple comparisons cannot be ruled out. History of hysterectomy and multiparity showed nearly significant associations with adenocarcinoma, but it is not clear how many other health history factors were also considered. Coal burning has been associated with lung cancer in several other studies. Similarly, as in several other studies, one found an association with low beta carotene intake, but there was no evidence of a dose-response gradient, and no significant association was found for preformed vitamin A. The strongest association with a dietary factor was actually that for low intake of dairy products and eggs, which showed a consistent dose-response pattern. The use of a matched-pair analytical approach controls for possible confounding due to age or neighborhood, which also reduces the likelihood of neighborhood-related factors such as socioeconomic status as major sources of bias. Confounding due to active smoking can be ruled out in the passive smoking results for adenocarcinoma and is not likely in regard to other factors given adjustment for this variable in all analyses. Likewise, the authors report that adjustment for childhood pneumonia, coal burning, and beta carotene intake did not alter their results. Strangely, however, no adjustment for dairy product and egg intake--the dietary factor with the most convincing association with lung cancer in their data--was carried out.

Overall, this study's results are consistent with a mild association between spousal and workplace ETS exposures and lung adenocarcinoma, although they support no such association for parental smoking. In addition, the study it raises childhood pneumonia, coal burning during early life, low intakes of beta carotene, and low intake of dairy products and eggs as potential moderate risk factors that should be considered by future studies. The results for squamous cell carcinoma are uncertain given the small number of nonsmoking cases available, and in all instances, they lack statistical significance due to sample size limitations. Thus, the study provides useful information on the relationship of adenocarcinoma of the lung with ETS and a number of other factors: information regarding squamous cell cancer is of much lower utility.

25010322H1

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

A.33. WUWI

A.33.1. Author's Abstract

"A case-control study of lung cancer involving interviews with 965 female patients and 959 controls in Shenyang and Harbin, two industrial cities which have among the highest rates of lung cancer in China, revealed that cigarette smoking is the main causal factor and accounted for about 35% of the tumors among women. Although the amount smoked was low (the cases averaged eight cigarettes per day), the percentage of smokers among women over age 50 in these cities was nearly double the national average. Air pollution from coal burning stoves was implicated, as risks of lung cancer increased in proportion to years of exposure to Kang and other heating devices indigenous to the region. In addition, the number of meals cooked by deep frying and the frequency of smokiness during cooking were associated with risk of lung cancer. More cases than controls reported workplace exposures to coal dust and to smoke from burning fuel. Elevated risks were observed for smelter workers and decreased risks for textile workers. Prior chronic bronchitis/emphysema, pneumonia, and recent tuberculosis contributed significantly to lung cancer risk, as did a history of tuberculosis and lung cancer in family members. Higher intake of carotene-rich vegetables was not protective against lung cancer in this population. The findings were qualitatively similar across the major cell types of lung cancer, except that the associations with smoking and previous lung diseases were stronger for squamous/oat cell cancers than for adenocarcinoma of the lung."

A.33.2. Study Description

The objective of this study was to evaluate the role of potential risk factors for lung cancer in Harbin and Shenyang, two cities among those with the highest mortality rate for lung cancer in China. Active smokers are included in the cases, so data on ETS subjects constitute a subset of the whole study.

Cases consist of female residents under age 70 newly diagnosed with primary lung cancer in about 70 participating hospitals in Harbin and Shenyang between 1985 and 1987. Controls are female residents randomly selected from the general population of these cities and frequency matched by 5-year age group to the age distribution of female lung cancer cases reported in the cities in 1983. Trained interviewers collected information on smoking habits, diet, cooking and heating practices, and other factors from subjects in face-to-face unblinded interviews.

A total of 1,049 qualifying cases were found, including both ever-smokers and never-smokers, of which 405 were diagnosed by histology, 309 by cytology, and 351 by radiology or clinical means. (Note: These diagnostic numbers do not total 1,049. The 351 figure may be

250103242

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

intended to be 251, which would give a total of 965 diagnoses, about the number of cases interviewed.) Of these, 85 either died prior to interview, refused to participate, or could not be located. Mean age of participating cases was 55.9 years, whereas that of the 959 controls was 55.4 years. Nonsmokers compose 417 of the interviewed cases and 602 of the controls.

A smoker is defined as a person who has smoked cigarettes for 6 months or longer, so a nonsmoker apparently may have smoked up to 6 months. Information on all types of tobacco products smoked was collected. Sources of ETS exposure include smoking by any household cohabitant and smoking by individuals (spouse, mother, and father) over the course of the subject's lifetime. Exposure at the workplace is also addressed. ETS exposure in the home is expressed in terms of cigarettes per day and number of years smoked; no units of measurement are used for workplace smoking. No checks on exposure data were undertaken. Marital status of subjects is not discussed. Of the cases with histological or cytological data, adenocarcinomas compose 310 (41.7%), squamous cell cancers 201 (28.9%), small and oat cell cancers 117 (16.8%), and large cell or unspecified types 66 (9.5%). No data on airway proximity or diagnostic breakdowns limited to nonsmokers are provided.

Statistical analyses of potential risk factors, including ETS, largely include data on active smokers and then adjust for the effect due to smoking by logistic regression, along with other potential confounders such as age, education, and location. These analyses indicate no increase in risk from household sources of ETS, with estimated relative risks of 0.8 (household cohabitants), 0.9 (spouse), 1.0 (mother), and 1.0 (father). The estimated risk for workplace exposure is nonsignificant (RR = 1.2). Restriction of analyses to ETS subjects alone (i.e., only the nonsmokers) produced similar results, with estimated relative risks of 0.7 for general cohabitant, 0.7 for spouse, 0.9 for mother, 1.1 for father, and 1.1 for workplace exposure. The ETS exposure from spousal smoking is significantly low (i.e., associated with a *decrease* in lung cancer by this analysis, as apparent from the confidence interval; RR = 0.7; 95% C.I. = 0.6-0.9).

The smoking-adjusted analyses indicate associations with lung cancer for several types of heating devices, including kangs (brick beds heated by pipes from the stove or by burners directly underneath), coal stoves, and heated brick walls or floors. The risk associated with the use of burning kangs (those heated by stoves underneath) shows an upward trend with years of use, becoming statistically significant at 21 or more years of use (RR = 1.5; 95% C.I. = 1.1-2.0). Significantly elevated risks are also associated with use of heated brick walls or floors (RR = 1.5 [1.1-2.1] for 1-20 years of use; RR = 1.4 [1.1-1.9] for > 20 years). Nonsignificant increases in risk are noted for use of kangs of all types, coal stoves, and coal burners; nonsignificant reductions in risk are indicated for noncoal stoves and central heat. Use of deep frying at least twice a month

250103243

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

and eye irritation during cooking are both significantly associated with lung cancer, as are regular intake of animal protein and fresh fruit. (Note: Multiple comparisons may be a factor for the apparent significance of some items, as discussed further in the next section.)

The authors find no overall association between lung cancer and ETS exposure. On the other hand, coal burning, exposure to cooking oil fumes, and chronic lung disease may all be risk factors. Consumption of beta carotene shows no evidence of a protective effect. Overall, active smoking is the major cause of lung cancer among women in the regions sampled.

A.33.3. Comments

The sample size is impressive, with ETS exposure data available for nearly 1,000 cases including smokers and over 400 cases when restricted to nonsmokers, thus providing substantial statistical power. All subjects are women recruited from two industrial cities in northeast China, reducing potential for complications due to regional or urban-rural differences. Nearly all of the hospitals in these cities were involved, all cases occurring in these hospitals were targeted, and the rate of participation among eligible cases was high; thus potential for selection bias is minimized. The effective case recruitment in combination with the use of general population controls maximizes generalizability of the study's results for northeast China. It would have been useful, however, to present the results for the two component study locations separately. Although coordinated in planning and execution, there are two separate study locations and the sources of heterogeneity between them tends to be obscured when results are combined.

Unfortunately, the study's results with regard to ETS are more limited than the strengths listed above might suggest. The inclusion of age, education, and location as control variables in all analyses is laudable, thus eliminating three sources of potential confounding. The attempt to control for potential sources of confounding that may be causally related to lung cancer by statistical methods, however, is less certain. Although some analysis was conducted with data for active smokers included, to the authors' credit they also analyzed data for ETS subjects alone (i.e., with the data for active smokers removed), which is the surest way to control for confounding by active smoking. Other potential causes of lung cancer (e.g., air pollution from coal-burning stoves, smokiness during cooking, and deep-fat frying foods) also need to be taken into account in an analysis of ETS. This cannot always be accomplished effectively by statistical methods, particularly when there are multiple risk factors to be taken into account that are variable, poorly measured, and possibly more potent risk factors than ETS may be.

At the risk of belaboring this point, as the reader is aware, a case-control study is ideally designed and executed under conditions where cases and controls are as comparable as possible

250103244

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

aside from the factor of interest, such as ETS exposure. The presence of other risk factors may tend to pollute and obscure, much like the contamination of a laboratory experiment. In this same sense, the presence of indoor sources of smoke other than ETS may contaminate an environment for measuring ETS effects because the non-ETS smoke likely contains many of the same carcinogens as ETS, and possibly in much larger quantities, depending on the relative levels of exposure. Other factors outside the home, such as workplace exposure to coal dust and to smoke from burning fuel that was reported more often in cases than controls, contribute to the potential confounding in a similar way. Consequently, a credible analysis of ETS requires being able to adjust for these likely confounding factors satisfactorily, and the ability to do that depends on reliable measures of exposure and the extent of confounding. That kind of statistical analysis is not given in the article, and it does not appear to have been possible, based on conversations with the authors (Wu-Williams and Blot) and the text of the article: "Despite the large size of our study, we were unable to clarify the magnitude of risks due to passive smoking, recognized as a cause of lung cancer around the world (U.S. DHHS, 1986). Perhaps in this study population the effects of environmental tobacco smoke was obscured by the rather heavy exposures to pollutants from coal-burning Kang, other indoor heating sources, and high levels of neighborhood air pollution (Xu et al., 1989)."

The multivariate analysis reported in the article reinforces the viewpoint that any ETS effect may be dominated by the presence of other risk factors. In that analysis, variables were allowed to enter a logistic regression model in the order of their explanatory value (a stepwise regression exercise in statistical terminology). The order of entry into the model is deep frying, eye irritation, pneumonia, household tuberculosis, burning kang, self-reported occupational exposure to burning fuel, passive smoking, and heated brick wall or floor. Passive smoking, in this exercise, is significant ($p < 0.05$) but in the direction of reducing lung cancer, not contributing to it. The 0.05 value, however is not fully meaningful as a significance level for ETS, because of the stepwise procedure used (the same data used in the construction of a model is used for testing variables in the model) and because of the likely confounding between ETS and other variables. Note, for example, that passive smoking entered the model ahead of heated brick wall or floor, which is highly significant when analyzed alone, whereas passive smoking is not.

The evidence for association of lung cancer with burning coal and deep frying foods is particularly provocative, as it indicates two factors that may play a substantial role in the etiology of lung cancer in northeast China and, hence, in other areas as well where such practices occur. The associations noted with other factors are also of interest, but their importance is undermined by the problem of multiple comparisons. In the table presenting results for dietary factors, for

05/15/92
250103245

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

example, 26 risk estimates are computed, 4 of which are significant at the 5% significance level (for a two-sided test, 2.5% level for the test of an effect), only one more significant finding than expected due to chance alone.

Being somewhat speculative, the use of cases age 70 and below may be a factor. Wells (1988) showed that about half of the female passive smoking deaths occur after age 70, for the studies included in that reference. If ETS is a risk for lung cancer and if individual susceptibility to lung cancer is a factor, some of the stronger risk factors such as coal burning and cooking oil may have caused lung cancer in the more susceptible subjects before passive smoking had a chance to exert itself.

In summary, this large and basically well-executed study observed no significant association between exposure to ETS from cohabitants, spouse, parents, or workplace and lung cancer. Lack of control for a number of other significant risk factors identified in the study undermines these results, however. The associations with coal burning for heat and oil frying are particularly notable. Use of the heating devices most strongly linked with lung cancer is presumably more common in colder northern regions, whereas stir frying may be more widespread in Asian communities, without regard to climate. Thus, this study was exploratory, designed to generate hypotheses rather than to test the specific hypothesis that ETS exposure is associated with lung cancer. It identifies a number of potential risk factors for consideration in future studies. The prevalence of these factors in the study population combined with the lack of analysis of their association with ETS exposure, however, renders the results for ETS inconclusive.

2501032246 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

APPENDIX B. METHOD FOR CORRECTING RELATIVE RISK FOR SMOKER MISCLASSIFICATION

B.1. INTRODUCTION

The purpose of this Appendix is to present the details of the method used in Section 5.2.2. to correct observed passive smoking relative risks for the systematic upward bias caused by misclassification of some smokers as never smokers. The method used is that proposed by A. J. Wells and W. F. Stewart (Wells, 1990). This Appendix covers: Section B.2) the principles of the method; Section B.3) how the method differs from those previously used by the National Research Council and P. N. Lee; Section B.4) the data used to calculate the misclassification factors and other parameters; Section B.5) the mathematical model used to calculate the corrected relative risks; and Section B.6) a numerical example to show how the method is applied in a practical case. Evidence is also presented indicating that the true downward corrections for smoker misclassification bias may be even smaller than those used in Section 5.2.2.

There is considerable literature on this topic and a history of controversy regarding the magnitude of the bias and whether it may explain the observed increase in lung cancer mortality due to ETS exposure. The NRC report on the health effects of passive smoking (NRC, 1986) delves into this topic in considerable detail. It concludes that bias is likely and estimates an adjustment for the summary relative risk from the combined results for all ETS studies. The NRC report further concludes that smoker misclassification does not account for the observed passive smoking risk. On the other hand, Lee in various publications (Lee, 1987b, 1988, 1990, 1991) has claimed that the smoker misclassification bias is large enough to explain most or all of the observed passive smoking lung cancer risk.

Approaches to estimation of misclassification bias have used mathematical modeling with parameters estimated from a variety of sources that have not always been consistent. The procedure described below attempts to rectify some previous sources of misunderstanding on this topic and utilizes the extensive data sources now available to improve parameter estimates and tailor refinements to individual populations.

250103247

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

B.2. PRINCIPLES OF THE WELLS-STEWART METHOD

The Wells-Stewart method is based on the following principles, the nature and need for which have largely become apparent from the chronological evolution and disparate approaches and results on this problem.

Parameters:

a. Limit the misclassifieds to those who said they never smoked, not simply to nonusers, because the latter would include self-reported former smokers, who are not a factor in the epidemiology.

b. Use one minus sensitivity or its close relative, false negatives (misclassified smokers) divided by observed positives (self-reported smokers) as the vehicle for transferring misclassification data from cotinine and discordant answer studies to the passive smoking studies. Sensitivity is the term used to describe the fraction correctly classified as exposed, namely true positives divided by true positives plus false negatives, but since we are assuming that the true positives and the observed positives are the same (no misclassification of never-smokers as smokers). Sensitivity in this case becomes observed positives divided by observed positives plus false negatives. Thence one minus sensitivity becomes false negatives divided by observed positives plus false negatives. Ignoring the false negatives in the denominator introduces negligible error. In any case do not use specificity (true negatives divided by true negatives plus false positives) or any parameter that uses as its denominator true or observed negatives (self-reported never-smokers). The reason is that sensitivity is affected much less by smoker prevalence than parameters based on observed negatives.

c. Calculate a correction for each epidemiologic study separately using a misclassified smoker relative risk and a proportion of smokers among subjects and spouses that is characteristic of the timeframe and locale of each study. Use data from the study itself or from another study with the same target population, if possible.

d. Use only female data to correct misclassification of female subjects.

Mathematical model:

Calculate the corrected risk directly--that is, do not first calculate a bias assuming no passive risk and then divide the observed risk by that bias to get a corrected risk.

250103224B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Subjects found to be misclassified as nonsmokers are categorized according to their true smoking status--former or current. Current smokers are further classified as "regular" or "occasional", according to cotinine levels observed. "Regular" means the cotinine level is above 30% of the self-reported smoker mean; "occasional" applies to the range 10-30%. Cotinine levels are not informative for misclassified former smokers, who tend to be long term abstainers (10+ years, according to Lee (1987b) and Wald et al. (1986)). The two studies with detailed cotinine levels on female current smokers (Lee, 1986 and Haddow et al., 1986, in Table B-1) indicate that about 10% of the current smokers are occasionals.

B.3. DIFFERENCES FROM EARLIER WORK

The Wells-Stewart method differs from the method used by the NRC (1986), which is also described by Wald et al. (1986), in that the NRC method failed to separate the misclassified smokers into regular, occasional, and exsmokers, and they failed to account for the effect of smoker misclassification on active smoker risk. The NRC made an overall correction to the aggregated passive relative risk using United Kingdom smoking prevalence and risk rather than making the corrections study by study with appropriate smoking prevalences and risk for each study's time and locale, and they mixed male data with female data in arriving at misclassification factors. Their calculated bias of 1.34/1.25 = 1.07, or 7%, for the combined worldwide studies is substantially higher than the 2% overall bias that would result if the biases in Table 5-7 were aggregated. The discrepancy is largely due to NRC's use of U.K. parameters for all of the studies regardless of locale, plus some overestimation of the impact of misclassified occasional and exsmokers.

Lee's methods have evolved over the years in three stages. In Lee (1987b, 1988) he improved on the NRC method in that he divided the misclassified smokers into exsmokers and current, regular and occasional smokers, and he corrected the smoker risk for misclassification. However, all of the five principles listed above were violated to some degree resulting in about a twelve-fold overestimation of the bias. The Lee (1990) paper correctly limits misclassifieds to never smokers, relates misclassified smokers to smokers, not to never smokers, and treats each study separately, but still mixes male input data with female data for use in calculating bias for females. Furthermore, his (Lee, 1990) mathematical model still relies on the assumption of no passive risk, which results in increased estimates of the bias as the observed relative risk increases. In addition, Lee (1990) has changed from separating the misclassified smokers into three groups in favor of the (less useful)

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

overall category of ever smokers. Most recently Lee (1991) presents a more complex mathematical model that includes a term for passive risk, but the method still has the other shortcomings noted for Lee (1990). A comparison of the most recent Lee bias estimates with those in Table 5-7 is shown in Table B-2 for the five U.S. studies with the greatest statistical weight. When Lee's inputs are used with the Wells-Stewart mathematical model, the calculated biases are if anything somewhat larger than when using Lee's most recent model. Therefore, the difference between Lee's most recent estimates of bias and those shown in Table 5-7 are in practical terms due almost entirely to differences in input parameters. The input parameters we have chosen are developed in the next section, and comparison with the Lee parameter estimates are shown as footnotes to Table B-2.

B.4. PARAMETER ESTIMATES

The key input into these calculations is the proportion of misclassified regular current smokers who claim they have never smoked. Our definition of misclassified regular current smokers, first suggested by Lee (1987b), produces a mean cotinine level approximately equal to that of all self-reported current smokers. Detailed data from three large cotinine studies have been assembled for use herein with the cooperation of their principal investigators (Coultas, Cumming, and Pierce in Table B-3). The data identify individual nonsmokers with cotinine values greater than 10% of the mean for self-reported smokers, by sex and self-reported smoking status (never or former). Data on nonusers are also available from several other studies (the lower portion of Table B-3). Since the numbers of misclassified smokers are small, the proportions of misclassified smokers who would have said "never" versus "former" are estimated using the proportions observed in the first three studies. Data sets not differentiating outcomes by sex have not been used. Also the large 1986 study by Haddow and colleagues has not been used for this purpose on the advice of one of the authors (private communication from G.J. Knight).

The number of self-reported never- and former smokers with sufficiently high cotinine levels to be reclassified as current smokers is shown by study in Table B-3. As described above, those with cotinine levels in the 10-30% range are considered to be occasional smokers while those above 30% are treated as regular smokers. If it is assumed that 90% of 1,525 self-reported current smokers, or 1,372, are regular smokers, leaving 10%, or 153, as occasionals, then the percentage of current regular smokers misclassified as never-smokers totalled over all studies in Table B-3 is 14/1,372 or 1.02%. The percentage is almost the same if the number of true, i.e., self-reported plus misclassified current

2501032250

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

regular, smokers is used. For the occasional smokers only, the misclassification rate is much higher, about 20% (15%) of observed (true) occasional smokers. It is possible, however, that the subjects classified as occasional smokers based on cotinine levels in the range 10-30% may contain some true never-smokers that are just highly exposed to passive smoke.

The studies in Table B-4 provide data on discordant answers, i.e., reported never-smokers who have called themselves smokers on one or more previous occasions. Based on those data, the estimated percentage of former smokers misclassified as never-smokers is about 12% (11%) of the observed (true) number of former smokers. As mentioned previously, evidence suggests (Wald et al., 1986; Lee 1987b) that most former smokers misclassified as never-smokers have been nonsmokers for an extended period, such as 10+ years, and may have been light smokers on average. Accordingly, we have used a weighted average of the data of Alderson et al. (1985), Lubin et al. (1984), and Garfinkel and Stellman (1988) for 10+ year abstainers to estimate former smoker relative risk, namely, an excess risk that is 9% of current smoker excess risk.

Some confusion and misleading conclusions on smoker misclassification have resulted from the practice of expressing the number of smokers misclassified as never-smokers as a percentage of the total number of (either true or observed) never-smokers, rather than as a percentage of the number of smokers. That leads to a higher expected percentage of smokers misclassified as never- smokers among cases than controls because lung cancer cases are much more likely to have been smokers than never-smokers. Some people have interpreted a higher percentage of observed never-smokers later found to be misclassified smokers among the cases as evidence that smokers with lung cancer are more apt to claim falsely to be never-smokers than persons without cancer. That conclusion, however, appears to be an artefact of treating the misclassification rate as a percentage of the number of never-smokers rather than as a percentage of the number of smokers. The study data summarized in Table B-5 do not support that conclusion. If anything, it is more supportive of the conclusion that ever-smokers in lung cancer studies may be less likely to misrepresent themselves as never-smokers than members of the general public who are questioned in community surveys. The one percent average misclassification rate shown in Table B-5 for the lung cancer cases suggests that estimates such as the 5.7% from the general population studies (Table B-5) or the near four percent of ever-smokers (Table B-4) that we have used may be much too high.

Further corroboration that the misclassification rates from the community studies are too high relative to those in the epidemiologic studies is found in the recent study by Fontham et al. (1991).

2501032251

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

After eliminating possible smokers among the self-reported never-smokers by the usual epidemiologic techniques, the investigators found by cotinine measurements that only two probable occasional smokers and no probable regular smokers were left among the 239 never-smoking lung cancer cases for which cotinine measurements were made. Assuming 45% ever-smoking among controls and an ever-smoker relative risk of 8 for regular smokers and 2.4 for occasionals, there would have been 1,456 smoker cases, consisting of 1,409 current smokers and 47 occasional smokers. It is seen that a misclassification rate of 0/1,409 = 0.00% for regular smokers is well below the 1.0% that we have used from the community surveys, and 2/47 = 4.3% for occasionals is also well below the 19.6% for occasionals that we have used.

Another indication that the estimates based on community surveys may be too high comes from analysis of male data. The observed percentage of never-smokers is typically much lower for males (17% to 35%) than females (41% to 86%). To correct for smoker misclassification we set up a deletions table analogous to Table B-15 where the number of current and former smokers misclassified as never-smokers are subtracted from the reported number of never-smokers. When the misclassification rates generated from community surveys are applied to the male data, the outcome is not credible--the number deleted for misclassification exceeds the total number of reported never-smokers in three of the eleven examples of which we are aware and drives the corrected relative risk well below unity in four more. This outcome indicates that the misclassification rates derived from the community surveys are too high. It is probable that the true smoker misclassification bias is on the order of one-fourth to one-half of the values shown in Table 5-7.

It is also said that East Asian women misclassify themselves at much higher rates than Western women. The data from the International Agency for Research on Cancer in Table B-3 do not support that claim, however, because the East Asia (Hong Kong, Japan, and China) misclassification rate for current regular smokers is 1/77 = 1.3%, not much different from the overall rate of 1.0%.

The main proponent of the idea that smoker misclassification accounts for most or all of the observed passive smoking risk has been P.N. Lee (1986, 1987b, 1988). He has estimated the bias for females to be as high as 1.24. However, his methods are open to considerable question. He used "nonuser" cotinine data, which includes people who said or would have said they were former smokers, rather than using only data on people who said they never smoked. This would about double the calculated bias. He averaged high male misclassification rates into low female misclassification rates. He made an overall correction to the combined risk using modern U.K. smoker risk and

2501032252

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

smoking prevalence rather than making the corrections study by study, as is done here with smoker risks and prevalence appropriate for each study. He transferred misclassification rates from the cotinine and discordant answer studies using percent of never-smokers rather than percent of smokers. He also used as an input the data from the large Haddow study (Haddow et al., 1987) when the authors state (private communication from Dr. George Knight) that the data from the study should not be used for misclassification studies. Also Lee's mathematical method tends to overstate the bias for passive risks greater than about 1.3. At a risk of two, his method overstates the bias about 100%.

In conclusion, it would appear that the bias introduced by misclassification of smokers as never-smokers is not a serious problem. It probably increases perceived relative risks on a worldwide basis by 1% to 2%, with the effect being about three times as large for combined U.S. studies.

B.5. MATHEMATICAL MODEL

The proportion of observed smokers, m_{h0}, misclassified as never-smokers is estimated separately for former smokers (m_{10}), occasional smokers (m_{20}), and regular smokers (m_{30}). Similarly, the proportion of observed current smokers, m_{h1}, misclassified as former smokers is estimated separately for occasional smokers (m_{21}) and regular smokers (m_{31}). These estimates are given in Tables B-3 and B-4. It is assumed that there is no misclassification of true never-smokers as current or former smokers or of observed former smokers as current smokers. Also these misclassification factors are used for all the studies unless otherwise noted. We suspect that misclassification rates probably vary from study to study. That variability, however, would tend to cancel out as the individual study results are combined.

Let c_{ijk} designate the observed proportionate distribution of controls (i = 0) and cases (i = 1) by their smoking status (j = 0,1,2,3) and the smoking status of their husbands (k = 0,1) as illustrated in Table B-6. Following the notational convention that a dot in the subscript position means summation on that subscript, then $c_{0..} = c_{1..} = 1$.

The observed c_{ijk}'s are corrected for misclassification of the wife's smoking status by first specifying a 4 x 4 matrix of proportionate distribution (Table B-7), where P_{hj} (h,j = 0,1,2,3) is the probability that a subject with true smoking status h will also be observed to have smoking status j. The subscripted notation is shown in Table B-7 for easy reference. P.. is equal to unity.

For passive smoking, we are interested only in correcting the c_{i0k} values that are for the observed never-smokers. It is assumed that the P_{hj}'s are the same for cases and controls

250103225

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

(nondifferential misclassification). For given values of wife's subject status (i) and husband's smoking status (k), the correction when the wife's observed smoking status is "never" (j = 0), is:

$$C_{i0k} = c_{i0k} - \sum_{h=j=1}^{3} c_{ijk} \, (p_{h0} / p_{\cdot j}) \qquad \text{(B-1)}$$

where C_{i0k} is the corrected form of the element of the element c_{i0k}. Then the corrected passive risk, RR(c), becomes:

$$RR(c) = C_{101} \times C_{000} / C_{100} \times C_{001} \qquad \text{(B-2)}$$

The values of c_{0jk} in Table B-6 are from prevalence data in the study itself or from a related study, from concordance data, and from each study's data on the smoking prevalence of the never-smokers' husbands. If necessary, the number of former smokers can be estimated from the ever-smokers based on data from nine studies known to us where the percent of both current smokers and former smokers is known (see Table B-16). These data indicate a time trend in nontraditional societies, from 17% former smokers relative to ever-smokers in 1960 to 45% in 1985; we estimate a 20-year lag for the traditional societies such as Hong Kong, China, Japan, and Greece. However, there are no data to support this assumption.

To calculate the individual elements, c_{0jk}, of Table B-6, it is necessary to establish concordance factors--that is, the cross products in 2 x 2 tables of smoking status of husbands and wives by smoking level of the wives. Using data from Sutton (1980), Lee (1987b), Akiba et al. (1986) and Hirayama (1984) and the detailed data in Lee (1987b) on never-smokers, current smokers, and former smokers, we have calculated that an appropriate average concordance factor for current smoking wives and ever-smoking husbands versus never-smoking wives and never-smoking husbands is 3.2; for ever-smoking wives and husbands versus never-smoking wives and husbands, it is 2.8, and for former smoking wives and ever-smoking husbands versus never-smoking wives and husbands, it is 2.2. These concordance factors can be expected to vary from study to study, but the effect of the variability should tend to cancel out as the studies are aggregated. The element $c_{00\cdot}$ and a quantity $s_0 = \sum_{j=1}^{3} c_{0j\cdot}$

2501032254

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

are obtained from smoking prevalence data in the study itself, in a related study on the same cohort, or as a last resort from national statistics. The elements c_{01}. and c_{02}. + c_{03}. are taken from the study or are estimated from Table B-16. Element c_{02}. is estimated to be 10% of (c_{02}. + c_{03}.); c_{03}. is 90%. Elements c_{000} and c_{001} are obtained from c_{00}. and the proportion of never-smoking controls in the study who are married to either never-smokers or ever-smokers. Elements c_{010} and c_{011} are obtained by solving the equations $c_{010} + c_{011} = c_{01}$. and $c_{000} \times c_{011} / c_{001} \times c_{010} = 2.2$. Terms $s_{00} = \sum_{j=1}^{3} c_{0j0}$ and $s_{01} = \sum_{j=1}^{3} c_{0j1}$ are obtained from the equations $s_{00} + s_{01} = s_0$ and $s_{01} \times c_{000}/c_{001} \times s_{00} = 2.8$. Then $c_{020} + c_{030} = s_{00} - c_{010}$ and $c_{021} + c_{031} = s_{01} - c_{011}$. The values of c_{020} and c_{021} are then assumed to be 10% of $c_{020} + c_{030}$ and $c_{021} + c_{031}$, respectively, and c_{030} and c_{031} are assumed to be 90%.

To obtain the elements for the subject cases (i = 1) in Table B-6, it is necessary first to set up relative risks for the passively exposed (k = 1) and not passively exposed (k = 0) wives by observed smoking status (j = 0,1,2,3). These risks are shown in Table B-8.

In most instances, the relative risk, RR(e), for female ever-smokers can be obtained from the study itself or from a related paper (Table B-9). In a few instances, it is necessary to estimate RR(e) from other studies similar in time and locale. In some papers, a current smoker risk also is given. We assume (based on cotinine measurements) that the misclassified regular smoker risk, $RR(a)_3$, is equal to the self-reported current smoker risk. Where only RR(e) is available, $RR(a)_3$ can be assumed to be equal to 1.24 x RR(e) based on the data in Table B-17. Because occasional smokers have cotinine levels that are 10% to 30% of those of regular smokers, it is assumed that $RR(a)_2 - 1 = 0.20(RR(a)_3 - 1)$, and because the former smokers (j = 1) are said to be, on average, long term (Wald et al., 1986; Lee, 1987b), we have averaged the data of Alderson et al. (1985), Lubin et al. (1984), and Garfinkel and Stellman (1988) for 10+ year former smokers, namely, that $RR(a)_1 - 1 = 0.09\ (RR(a)_3 - 1)$.

The elements RR_{00} and RR_{01} are obtained from the observed passive relative risk in the study and the never-smoking population weights for controls in Table B-6 by solving the equations

$$(RR_{00} \times c_{000}) + (RR_{01} \times c_{001}) = 1.00$$

and

2501032255

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

$$RR_{01} / RR_{00} = RR(p)_0.$$

Other assumptions regarding passive risks can be used for j = 1,2, and 3. We have assumed, based on the data in Varela (1987) who found that 242 long-term former smokers had essentially the same passive risk as 197 never-smokers, that the passive risk for former smokers to be the same as for never-smokers, namely, that $RR(p)_1 = RR(p)_0$. It is also assumed that there is no passive risk for current or occasional smokers so $RR(p)_2$ and $RR(p)_3$ are unity.

Crude versions of the elements c_{1jk} (i = 1 for cases) are obtained by multiplying each element c_{0jk} by its respective RR_{jk}. These are then normalized to give

$$c_{1jk} = \frac{c_{0jk} RR_{jk}}{\sum_{j=0}^{3} \sum_{k=0}^{3} c_{0jk} RR_{jk}}$$

The next step is to set up Table B-7, which is the table of proportionate distribution. This is done by multiplying the observed misclassification rates ($P_{h0}/P_{.j}$) from footnotes 2 and 4 in Tables B-3 and B-4, respectively, by the appropriate elements from Table B-6. For example, $P_{10} = C_{01}.(P_{10}/P_{.1})$. An attempt was made to use the true misclassification rates from Tables B-3 and B-4 on the theory that they would exhibit less variability in being transferred from the cotinine and discordant answer studies to the passive smoking calculations. However, the method is laborious and, as is shown in the Correa example below, does not lead to increased accuracy.

The next step is to develop a deletions table to implement Equation B-1, above, using the control and case smoking prevalences in Table B-6 and the proportionate distribution in Table B-7. Each observed element, c_{i0k}, in Table B-6 is multiplied by its appropriate observed misclassification factor, $P_{h0} / P_{.j}$, where h = j, to yield a deletion element to be subtracted from the appropriate observed wives' never-smoking-status elements: c_{000}, c_{001}, c_{100}, and c_{101}, to obtain corrected elements C_{000}, C_{001}, C_{100} and C_{101}. Thus, $C_{000} = c_{000} - \sum_{h=j=1}^{3} c_{0j0} P_{h0}/P_{.j}$, etc.

Once these corrected never-smoker elements are obtained, the relative risk corrected for smoker misclassification is obtained from Equation (B-2); $RR(c)_0 = C_{101} \times C_{000}/C_{100} \times C_{001}$, and the bias becomes $RR(p)_0 / RR(c)_0$.

2501032256

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

B.6. NUMERICAL EXAMPLE

Using the Correa study as an example, the study tells us that 52.8% of the wives never smoked and that 45.9% of the never-smoking wives were exposed to their spouses' smoke. This establishes $c_{00\cdot}$ as 0.528 and c_{000} and c_{001} as 0.286 and 0.242, respectively. The quantity $s_{0\cdot}$, the proportion of ever-smokers, by difference is 0.472. Assuming (from Table B-16) that the former smokers are 35.5% of the ever-smokers, the former smokers, $c_{01\cdot}$, become 0.167, and the current smokers ($c_{02\cdot} + c_{03\cdot}$) become 0.305. The current smokers are divided into current regular smokers at 90% ($c_{03\cdot} = 0.275$) and current occasional smokers at 10% ($c_{02\cdot} = 0.030$). These data are shown in the bottom line of Table B-10.

Using the concordance factor of 2.8 for ever-smokers versus never-smokers, it is possible to show algebraically that 33.2% of the females in the Correa study would be ever-smoker wives with smoking husbands (s_{01}) and that 14.0% would be ever-smoker wives with never-smoking husbands (s_{00}). Similarly, using the concordance factor of 2.2 for former smoking wives and ever-smoking husbands versus the never-smokers, the former smoking wives married to ever-smoking husbands (c_{011}) would be 10.9% of the total and those married to the never-smoking husbands (c_{010}) would be 5.8%. Then by difference, exposed current smoking wives ($c_{021} + c_{031}$) would be 22.3%, to be split into 20.1% regular smokers (c_{031}) and 2.2% occasional smokers (c_{021}), and the nonexposed current smoking wives ($c_{020} + c_{030}$) would be 8.2%, split into 7.4% regular smokers (c_{030}) and 0.8% occasional smokers (c_{020}). These data now supply all the elements needed in Table B-10 and the control part of Table B-6.

The relative risk for passive smoking, $RR(p)_o$, for females is 2.07 (Correa et al., 1983). The age- and sex-adjusted relative risk for current smoking from a related paper (Correa, 1984) is 12.6. The ratio of female smoking crude risk to the average for males and females is about 80%, indicating an age-adjusted current female risk of about 10. (Note: This is different from the current smoker relative risk that would be calculated from the crude ever-smoker risk of 12.4 used in Table 5-7 [of this report] and Table B-3. The adjusted risk is used here simply as an example.) With these inputs and the weights of controls in the study, the various exposed and nonexposed relative risks are those shown in Table B-11. The weighted average risk for the occasional smokers is calculated as 0.20 (current regular risk - 1) + 1, which for this example is 0.20 (10 - 1) + 1 = 2.80. The weighted average risk for former smokers is 0.09 (current regular risk - 1) + 1, which is 0.09 (10 - 1) + 1 = 1.81. The weighted average risks are split between never-smoking and ever-smoking husbands by

250103257

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

using the passive risks and the population weights. A crude case prevalence table is then made up (Table B-12) by multiplying each c_{0jk} by its respective RR_{jk}. This table is then normalized by dividing through by 3.665 to yield Table B-13, which is the lower half of Table B-6 for this example.

The proportionate distribution table (Table B-14) is developed, as described above, from the misclassification factors in Tables B-3 and B-4 and the bottom line of Table B-10. For example, to arrive at element (h = 3, j = 0) the observed $P_{\cdot 3}$ of 0.275 is multiplied by an observed misclassification factor of 0.0102 (from Table B-3 of this report) to yield 0.00281, which rounds to 0.003. To explore the value of using the true misclassification factors instead of the observed ones, the true and observed m's were carried to five decimal places. An approximation procedure to determine the true smoking probabilities $P_{0\cdot}$, $P_{1\cdot}$, $P_{2\cdot}$, and $P_{3\cdot}$ was carried through four stages. The resulting total true distribution of smoking status, 0.49987, 0.18040, 0.03893, and 0.28081, rounded to three decimal places is essentially identical to the distribution shown in the bottom line of Table B-14. Similarly, any differences in the individual elements were very small and beyond the accuracy of the underlying data. The Correa study was chosen as our example because the female ever-smoking prevalence is reasonably high (47.2%) and the female current smoker lung cancer relative risk is high (10), both factors that should lead to a greater rather than a smaller correction to the passive risk.

We now can set up a deletions table, Table B-15, which is the equivalent of Equation 1 above, by multiplying the control and case elements in Table B-10 and B-13 by the appropriate observed misclassification rates $P_{h0}/P_{\cdot j}$ (h = j), namely, $P_{10}/P_{\cdot 1} = 0.117$, $P_{20}/P_{\cdot 2} = 0.196$, and $P_{30}/P_{\cdot 3} = 0.01020$. For example, to get 0.00678, one multiplies 0.058 from Table B-10 by 0.117. Then the first three columns are summed horizontally to get the fourth column which is then subtracted from the elements in the "never" columns of Tables B-10 and B-13 (column 5) to get the "corrected never" elements (column 6).

The corrected passive risk is now obtained by taking the cross product from the "corrected never" column: 0.07516 x 0.27690/0.04705 x 0.22308 = 1.984, which is to be compared with the observed risk of 2.07. The bias is then 2.07/1.984 = 1.044. It is interesting to note how sensitive the bias is to the smoker relative risk that is assumed. When the crude smoker risk (no age adjustment) of 12.4 for ever-smokers, equivalent to about 15.4 for current regular smokers, is assumed, the corrected passive risk is 1.90, and the basis is twice as great at 1.09.

2501032258

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-1. Observed ratios of occasional smokers to current smokers (based on cotinine studies)

Study	Females			Both Sexes[3]		
	Occ'l	Current	Occ'l/Current	Occ'l[1]	Current	Occ'l Current
Lee (1986)	4	72	0.056	12	176	0.068
Coultas et al. (1988)				59	278	0.212
Haddow et al. (1986)	10	64	0.156			
Feyerabend (1982)[2]				7	82	0.085
Jarvis (1987)				12	90	0.133
Pojer (1984)				25	187	0.134
Wald et al. (1984)				13	131	0.099
Overall	14	136	0.103	128	944	0.136

[1] Occasional smokers are defined as persons who have cotinine levels in body fluids that are between 10% and 30% of the mean of all self-reported current smokers.

[2] The Feyerabend (1982) data are for nicotine.

[3] The "Both Sexes" data are shown to indicate that the female value of 10.3% is not unduly high.

250103259

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-2. Differences in smoker misclassification bias between EPA estimates and those of P.N. Lee regarding passive smoking relative risks for females

Study	% of U.S. Weight	Lee (1991 Model)[1]			Wells-Stewart Model					
		Lee (1991) Input Parameters			Lee (1991) Input[2] Parameters			EPA Input Parameters (Table 5-7)[2]		
		RR_o	RR_c	Bias	RR_o	RR_c	Bias	RR_o	RR_c	Bias
FONT	35	1.32	1.17	1.13	1.32	1.14[3]	1.15	1.29	1.26[3]	1.03
GARF (Coh)	25	1.17	1.02	1.15	1.17	0.99[4]	1.19	1.17	1.15[4]	1.02
GARF	15	1.23	1.09	1.13	1.23	1.06[5]	1.17	1.31	1.24[5]	1.06
JANE	10	0.75	0.65	1.15	0.75	0.62[6]	1.22	0.86	0.78[6]	1.10
CORR	3	2.07	1.63	1.26	2.07	1.47[7]	1.41	2.07	1.90[7]	1.09

Note: Calculated bias is very sensitive to three key factors, high values of which will drive the bias up; namely, fraction of observed never smokers misclassified, female active smoker relative risk and female smoking prevalence. Lee's inputs are higher than EPA's as indicated in footnotes 2-7. RR_o = observed passive risk. RR_c = passive risk corrected for smoker misclassification bias. Bias = RR_o/RR_c.

[1] Multiplicative model, Lee's Table 3.

[2] EPA's misclassification factors developed in Section B.4., namely, 1.02% of current regular smokers, 19.6% of current occasional smokers, and 11.7% of ex-smokers, when weighted for their respective prevalence and relative risk, are equivalent to about 1.5% of average self-reported ever smokers. EPA used these rates for all studies except FONT which is a special case. Lee used 2.0% for all studies.

[3] All current smokers, regular plus occasional, were eliminated from the analysis based on cotinine test data. This results in a misclassification factor of 0.5% of ever smokers. Lee's 49% ever smokers is higher than 1985 U.S. statistics value of 42%.

DRAFT--DO NOT QUOTE OR CITE

250103260

05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

DRAFT--DO NOT QUOTE OR CITE

Table B-2. (continued)

[4] A female smoker risk of 3.58 (U.S. DHHS, 1986) and smoker prevalence of 32% (Hammond, 1966) are considered standard for this study. Lee used 8.0 and 49%.

[5] EPA estimates a smoker risk of 6 and a smoking prevalence of 46% for the time period 1971-81 vs. Lee's values of 8.0 and 49%.

[6] The main difference is in the assumed smoker misclassification rate but Lee's assumption of 49% smoking prevalence vs. 46% assumed by EPA increases the bias estimate by about 3%.

[7] Lee assumed 58% smoking prevalence vs. 47% which EPA got from the paper itself. Lee assumed a lower smoker risk (9.5) vs. EPA's 12.4; the effect of this was offset by Lee's assumption of a multiplicative model for smoker's passive risk vs. EPA's assumption of no passive risk for smokers.

05/15/92

2501032261

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-3. Misclassification of female current smokers

Study	Cotinine Level[1]	Self-reported Smoking Status: Never[2]	Former[2]	Current
Coultas et al. (1988)	10-30	7	3	
	30+	5	8	
	All	387	79	184
Cummings (1990)	10-30	0	1	
	30+	2	0	
	All	225	143	116
Pierce et al. (1987)	10-30	9	4	
	30+	3	3	
	All	232	79	167
Subtotal	10-30	16	8	(67% never)
	30+	10	11	(48% never)
	All	844	301	467
Lee (1986)[3]	10-30	3	2	
	30+	2	3	
	All	333	125	256
Haddow et al. (1986)[3]	10-30	1	1	
	30+	0	1	
	All	174	58	64
Haddow et al. (1988)[3]	10-30	8	4	
	30+	1	0	
	All	1,128	380	503
Riboli (1991)[3]--US[4]	10-30	1	0	
	30+	0	0	
	All	224	81	143
Riboli (1991)[3]--East Asia[5]	10-30	1	1	
	30+	1	0	
	All	325	25	77
Riboli (1991)[3]--Greece[6]	10-30	0	0	
	30+	0	0	
	All	96	5	15
Total	10-30	30	16	
	30+	14	15	
	All	3,124	975	1,525

2501032262

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-3. (continued)

[1] Cotinine levels are in units of percents of the mean of self-reported smokers for each study; 30+% are defined as current regular smokers, 10-30% are occasional smokers.

[2] The observed current smokers are assumed to be 90% regular (1,372) and 10% occasional (153) smokers. For regular smokers, misclassification as never-smokers is 14/372 = 1.02% of observed current regulars or 14/(1,372 + 14 + 15) = 1.00% of true current regulars. For occasional smokers, misclassification is 30/153 = 19.6% of observed current occasionals or 30/(153 + 30 +16) = 15.1% of true current occasionals. For current smokers misclassified as former smokers the factors are 15/1,372 = 1.09% for observed and 15/1,401 = 1.07% for true regular smokers, and 16/153 = 10.5% for observed and 16/199 = 8.0% for true occasionals.

[3] For Lee (1986), Haddow et al. (1986), Haddow et al. (1988), and Riboli (1991), there was no breakdown given between "Never" and "Former", because the numbers are small, an estimate was made based on the subtotal distribution. The number of smokers had to be estimated in some cases.

[4] New Orleans, Los Angeles, and Honolulu.

[5] China (Shanghai), Hong Kong, and Japan (Sendai).

[6] Athens.

2501032263

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-4. Misclassification of female former smokers reported as never-smokers based on discordant answers

Study	Locale	Former Smokers (FS)[1]	Ever-Smokers (ES)[1]	Reported never-smokers who reported earlier that they had smoked[1]		
				N	Percent of ES	Percent of FS
Kabat and Wynder (1984)[5]	U.S.					
Controls		109	319	0	0.0	0.0
Cases		222	652	7	1.1	3.2
Machlin et al. (1989)	U.S.	194	687	52	7.6	26.8
Krall et al. (1989)[2]	Mass.	11	30	1	3.3	9.1
Britten (1988)[3]	U.K.	320	878	38	4.3	11.9
Lee (1987b)	U.K.	85	243	13	5.5	15.3
Akiba et al. (1986)	Japan	8	38	0	0.0	0.0
Overall[4]		949	2847	111	3.9	11.7

[1] Number of former smokers and ever-smokers had to be estimated in some cases.
[2] Krall data are based on 20-year recall.
[3] Britten data include only those persons who said they never smoked but actually had smoked regularly one or more cigarettes per day.
[4] For former smokers, misclassification as never-smokers would appear to be 111/949 = 11.7% of observed former smokers or 111/(949 + 111) = 10.5% of true former smokers, but from Table B-3 16 + 15/(16 + 15 + 975) = 3.08% of former smokers are really current smokers, so the 949 + 111 = 1,060 should be reduced by 3.08% to 1,027 as the number of true former smokers. Then 111/1,027 = 10.81% based on true former smokers.
[5] Dr. Kabat (private communication) advised that of 13 misclassifieds, 8 were females, 1 of whom used snuff.

05/21/92
2501032264

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-5. Misclassification of female lung cancer cases

Source	Number of Ever-smokers	Number Misclassified
CHAN Chan et al. (1979)[1]	12	1
KABA Kabat and Wynder (1984)[2]	652	7
AKIB Akiba et al. (1986)	38	0
PERS Pershagen et al. (1987)	179	2
HUMB Humble et al. (1987)[3]	223	1
Total	1,104	11 (1%)
General Population[4]	1,838	104 (5.7%)

[1] Chan sampled five Type I and II never-smokers, one of whom was said by a relative to have smoked a few hand-wrapped cigarettes for a year at age 71. The ratio of smoking to nonsmoking cases for Types I and II was 44/19, which, multiplied by 5, leads to 12 estimated ever-smokers.
[2] Dr. Kabat (private communication) advised that of 13 misclassifieds, 8 were females, 1 of whom used snuff.
[3] Of the four misclassifieds found, Dr. Humble (private communication) has advised that most if not all were males. We have assumed one female.
[4] The general population data are taken from the four nonlung cancer cohorts in Table B-4, namely, Machlin (1989), Krall (1989), Britten (1988), and Lee (1987b).

250103265

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-6. Notation for proportionate distribution of reported female lung cancer cases and controls by husband's smoking status

		Wife's Observed Smoking Status (j)				
Wife's Subject Status (i)	Husband's Smoking Status (k)	Never (j = 0)	Ex (j = 1)	Occ'l (j = 2)	Reg (j = 3)	Total
Control	Never (k = 0)	c_{000}	c_{010}	c_{020}	c_{030}	$c_{0\cdot0}$
(i = 0)	Ever (k = 1)	c_{001}	c_{011}	c_{021}	c_{031}	$c_{0\cdot1}$
	Total	$c_{00\cdot}$	$c_{01\cdot}$	$c_{02\cdot}$	$c_{03\cdot}$	$c_{0\cdot\cdot}$ (= 1)
Case	Never (k = 0)	c_{100}	c_{110}	c_{120}	c_{130}	$c_{1\cdot0}$
(i = 1)	Ever (k = 1)	c_{101}	c_{111}	c_{121}	c_{131}	$c_{1\cdot1}$
	Total	$c_{10\cdot}$	$c_{11\cdot}$	$c_{12\cdot}$	$c_{13\cdot}$	$c_{1\cdot\cdot}$ (= 1)

250103266

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-7. Proportionate distribution notation for subjects by observed and true smoking status

Wife's Observed Smoking Status (j)	Wife's True Smoking Status (h)				
	Never (h = 0)	Former (h = 1)	Occ'l (h = 2)	Reg. (h = 3)	Total
Never (j = 0)	P_{00}	P_{10}	P_{20}	P_{30}	$P_{\cdot 0}$
Former (j = 1)	P_{01}	P_{11}	P_{21}	P_{31}	$P_{\cdot 1}$
Occ'l (j = 2)	P_{02}	P_{12}	P_{22}	P_{32}	$P_{\cdot 2}$
Reg. (j = 3)	P_{03}	P_{13}	P_{23}	P_{33}	$P_{\cdot 3}$
Total	$P_{0\cdot}$	$P_{1\cdot}$	$P_{2\cdot}$	$P_{3\cdot}$	$P_{\cdot\cdot}(= 1)$

2501032267

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-8. Observed lung cancer relative risks for exposed and nonexposed wives by the wife's smoking status using average never-smoking wives as the reference category

	Wife's Smoking Status			
Husband's Smoking Status	Never (j = 0)	Former (j = 1)	Occ'l (j = 2)	Reg. (j = 3)
Never (k = 0)	RR_{00}	RR_{10}	RR_{20}	RR_{30}
Ever (k = 1)	RR_{01}	RR_{11}	RR_{21}	RR_{31}
Weighted avg. active risk	$RR(a)_0 = 1.00$	$RR(a)_1$	$RR(a)_2$	$RR(a)_3$
Passive risk[1] $RR(p)_j = RR_{j1}/RR_{j0}$	$RR(p)_0$	$RR(p)_1$	$RR(p)_2$	$RR(p)_3$

[1] Observed passive risk--the ratio of the exposed risk to the unexposed risk in each column.

05/21/92
2501032268

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-9. Prevalences and estimates of lung cancer risk associated with active and passive smoking[33]

Case-Control	Ever-smokers Prev. (%)[1]	Ever-smokers Crude RR[2]	Never-smokers Prev. of Exposed (%)[3]	Never-smokers Crude RR[2, 17]	Never-smokers Adj. RR[2, 4, 17]
AKIB	21	2.38 (1.67, 3.39)	70	1.52 (0.96, 2.41)	**1.5 (1.0, 2.5)**
BROW	29	4.30[23] (2.24, 8.24)	15	**1.52[23] (0.49, 4.79)**	*
			12	1.82[23] (0.45, 7.36)[7]	1.68[23] (0.39, 6.90)[7]
BUFF	59	7.06[15] (5.18, 9.63)	84	**0.81[15] (0.39, 1.66)**	*
CHAN	26	3.48 (2.42, 4.99)	47	**0.75 (0.48, 1.19)**	*
CORR	47	12.40 (8.35, 18.4)	46	**2.07[24] (0.94, 4.52)**	*
FONT[34]	42[21]	8.0[21]	63	1.37 (1.10, 1.69)	**1.29 (1.03, 1.62)**
			66	1.21 (0.94, 1.56)	1.28 (0.98, 1.66)
			64	1.32 (1.08, 1.61)	*
GAO	18	2.54 (2.06, 3.12)	74	**1.19 (0.87, 1.63)**	1.34[5,6]
GARF	*	*	61	**1.31 (0.93, 1.85)**	1.70[26] (0.98, 2.94)[7]
GENG	41	2.77[27] (1.89, 4.07)	44	**2.16** (1.21, 3.84)	*
HIRA[8]	16	3.20[9] (2.67, 3.83)	77	**1.53[5] (1.10, 2.13)**	1.64[5] *
HUMB	41	16.3 (10.5, 25.1)	56	2.34 (0.96, 5.69)	**2.2 (0.9, 5.5)**
INOU	16	1.66 (0.73, 3.76)	64	**2.55[16] (0.90, 7.20)**	2.54[5,10] *

25010326269

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-9. (continued)

Case-Control	Ever-smokers Prev. (%)[1]	Ever-smokers Crude RR[2]	Never-smokers Prev. of Exposed (%)[3]	Never-smokers Crude RR[2,17]	Never-smokers Adj. RR[2,4,17]
JANE	46[21]	8.0[21]	80	**0.86 (0.57, 1.29)**	0.93/0.44[11]
KABA[28]	42	5.90 (4.53, 7.69)	60	**0.79 (0.30, 2.04)**	*
KALA	17	3.32 (2.12, 5.22)	60	1.62[12] (0.99, 2.65) 1.41 (0.78, 2.55)	**1.92 (1.02, 3.59)[7]** *
KATA	28	1.21 (0.50, 2.90)	82	*[19]	*
KOO	32	2.77 (1.96, 3.90)	49	**1.55 (0.98, 2.44)**	1.64
LAMT	24	3.77 (2.96, 4.78)	45	**1.65 (1.22, 2.22)**	*
LAMW	22	4.12 (2.79, 6.08)	56	**2.51[20] (1.49, 4.23)**	*
LEE	60[29]	4.61[29]	68	**1.03 (0.48, 2.20)**	0.75/1.60[13]
LIU	0.05	*	87	0.74 (0.37, 1.48)	**0.77 (0.35, 1.68)**
PERS	37[21]	4.2[21]	43	1.28 (0.82, 1.98)	**1.2 (0.7, 2.1)[7]**
SHIM	21[21]	2.8[21]	56	**1.08[30] (0.70, 1.68)**	*
SOBU	21	2.81 (2.22, 3.57)	54	1.06[12] (0.79, 1.44) 1.77 (1.29, 2.43)	1.13[12] (0.78, 1.63)[7] **1.57 (1.07, 2.31)[7]**
SVEN	43	5.97 (4.11, 8.67)	66	**1.26[14] (0.65, 2.48)**	1.4[14]
TRIC	10	2.81[25] (1.69, 4.68)	52	**2.08[25] (1.31, 3.29)**	*

25010322270

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-9. (continued)

Case-Control	Ever-smokers Prev. (%)[1]	Ever-smokers Crude RR[2]	Never-smokers Prev. of Exposed (%)[3]	Never-smokers Crude RR[2, 17]	Never-smokers Adj. RR[2, 4, 17]
WU	58	4.38 (2.97, 6.47)	60	**1.41[18] (0.63, 3.15)**	1.2 (0.6, 2.5)[7]
WUWI	37	2.24 (1.92, 2.62)	55	**0.79 (0.64, 0.98)**	0.7
BUTL (Coh)	14[21]	4.0[21]	*	2.45[31]	**2.02 (0.48, 8.56)[7]**
GARF (Coh)	33[22]	3.5[22]	72	*	**1.17[5] (0.85, 1.61)[7]**
HIRA (Coh)	16	3.20[9] (1.96, 3.90)	77	**1.38 (1.03, 1.87)**	1.61 *
HOLE[32] (Coh)	56	4.2[21]	73	2.27 (0.40, 12.7)	**1.99 (0.24, 16.7)[7]**

[1] Percent ever-smokers in controls of whole study (or parent study).

[2] Parentheses contain 90% confidence limits, unless noted otherwise. Crude ORs and their confidence limits were calculated by the reviewers wherever possible. Boldface indicates values used for analysis in text of this report. OR for case-control studies; relative risk (RR) for cohort studies. The reference category for active smoking is all never-smoking, for passive smoking, it is unexposed never-smokers.

[3] Percent of never-smoking controls exposed to spousal smoking, unless noted otherwise.

[4] Calculated by a statistical method that adjusts for other factors (see Table 5-5).

[5] Composite measure formed from categorical data at different exposure levels.

[6] For Gao, data are given as (number of years lived with a smoker, adj. OR): (< 20, 1.0), (20-29, 1.1), (30-39, 1.3), (40+, 1.7).

[7] 95% confidence interval.

[8] Case-control study nested in the cohort study of Hirayama. OR for ever-smokers is taken from cohort study (shown in table below). This case-control study is not counted in any summary results where HIRA(Coh) is included.

[9] Crude OR is calculated from prospective data in Hirayama (1988). Adjusted OR for ever-smokers given there is 2.67 (no confidence interval [C.I.]).

[10] For Inoue, data are given as (number of cig./day smoked by husband, adj. OR): (< 19, 1.58), (20+, 3.09).

[11] From subject responses/from proxy responses.

[12] For the first value, "ETS exposed" means the spouse smokes; for the second value, "ETS exposed" means a member of the household other than the spouse smokes.

[13] From subject responses/from spouse responses.

[14] Exposure at home and/or at work.

250103271

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-9. (continued)

[15] Exposure to regularly smoking household member. Differs slightly from published value of 0.78, wherein 0.5 was added to all exposure cells.

[16] OR reported in study is 2.25, in contrast to the value shown that was reconstructed from the confidence intervals reported in the study; no reply to inquiry addressed to author had been received by press time.

[17] ORs for never-smokers applies to exposure from spousal smoking, unless indicated otherwise.

[18] Raw data for WU is from Table 11 of the Surgeon General's report (U.S. DHHS, 1986). Data apply to adenocarcinoma only.

[19] Odds ratio is not defined because number of unexposed subjects is 0 for cases or controls.

[20] Table entry is for exposure to smoking spouse, cohabitants, and/or coworkers; includes lung cancers of all cell types. The OR for spousal smoking alone is for adenocarcinoma only: 2.01 (90% C.I. = 1.20, 3.37).

[21] From other studies similar in location and time period (see Table 5-7).

[22] Prevalence is calculated from figures in Stellman and Garfinkel (1986) and includes all women except those who "never smoked regularly." RR is from U.S. Surgeon General (U.S. DHHS, 1982).

[23] Adenocarcinoma only. Data and OR value communicated from author (Brownson).

[24] Excludes bronchioalveolar carcinoma. Crude OR with bronchioalveolar carcinoma included is reported to be 1.77, but raw data for calculation of confidence interval are not provided.

[25] Known adenocarcinomas and alveolar carcinomas were excluded, but histological diagnosis was not available for many cases. Data are from Trichopoulos et al. (1983).

[26] Estimate for husband smoking 20 cigarettes per day.

[27] Crude OR reported in study is 3.05 (95% C.I. = 1.77, 5.30); adjusted OR is 2.6(95% C.I. = 1.4, 4.6).

[28] For second KABA study (see addendum in study description of KABA), preliminary unpublished data and analysis based on ETS exposure in adulthood indicate 68% of never-smokers are exposed and OR = 0.90 (90% C.I. = 0.51, 1.58), not dissimilar from the table entry shown.

[29] From Alderson et al. (1985).

[30] From crude data estimated to be the following: exposed cases 52, exposed controls 91, unexposed cases 38, unexposed controls 72.

[31] RR is based on person-years of exposure to spousal smoking. Prevalence in those units is 20%.

[32] RR values under never-smoker are for lung cancer mortality. For lung cancer incidence, crude RR is 1.51 (90% C.I. = 0.41, 5.48) and adj. RR is 1.39 (95% C.I. = 0.29, 6.61).

[33] Values used for inference in this report are shown in boldface. * means no information available.

[34] The first, second, and third entries are calculated for population controls, colon cancer controls, and both control groups combined, respectively. For adenocarcinoma alone, the corresponding ORs, both crude and adjusted, are higher by 0.15 to 0.18.

2501032272

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-10. Observed smoking prevalence among the controls--Correa example

Husband's Smoking Status	Wife's Smoking Status				
	Never	Former	Occasional	Regular	All
Never	0.286	0.058	0.008	0.074	0.426
Ever	0.242	0.109	0.022	0.201	0.574
All	0.528	0.167	0.030	0.275	1.000

Table B-11. Observed relative risks--Correa example

Husbands' Smoking Status	Wife's Smoking Status			
	Never (j = 0)	Former (j = 1)	Occasional (j = 2)	Regular (j = 3)
Never	0.67	1.07	2.80	10.0
Ever	1.39	2.21	2.80	10.0
Weighted Average	1.00	1.81	2.80	10.0
Passive Risk, $RR(p)_j$	2.07	2.07[1]	1.00[1]	1.00[1]

[1] Assumed.

250103227

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-12. Crude case table - prevalence of cases by smoking status--Correa example

Husband's Smoking Status	Wife's Smoking Status				
	Never	Former	Occasional	Regular	All
Never	0.192	0.062	0.022	0.740	1.016
Ever	0.336	0.241	0.062	2.010	2.649
All	0.528	0.303	0.084	2.750	3.665

Table B-13. Normalized case table - prevalence of cases by smoking status--Correa example

Husband's Smoking Status	Wife's Smoking Status				
	Never	Former	Occasional	Regular	All
Never	0.052	0.017	0.006	0.202	0.277
Ever	0.092	0.066	0.017	0.549	0.723
All	0.144	0.083	0.023	0.750	1.000

25010322?4

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-14. Proportionate distribution of observed and true smoking status for wives in Correa example[1]

Wife's Observed Smoking Status	Wife's True Smoking Status: Never (h = 0)	Former (h = 1)	Occasional (h = 2)	Regular (h = 3)	All
Never (j = 0)	0.500	0.020	0.006	0.003	0.528
Ex (j = 1)	0	0.161	0.003	0.003	0.167
Occ'l (j = 2)	0	0	0.030	0	0.030
Regular (j = 3)	0	0	0	0.275	0.275
All	0.500	0.180	0.039	0.281	1.000

[1] Values rounded to three decimal places.

250103275

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-15. Deletions from the never columns in Tables B-10 and B-13

Husband's Smoking Status		Wife's Smoking Status: Former (1)	Occ'l (2)	Regular (3)	Sum[1] (4)	Observed Never (5)	Corrected Never[2] (6)
Table B-10	Never	0.00678	0.00157	0.00075	0.00910	0.286	0.27690
(pop.)	Ever	0.01274	0.00433	0.00205	0.01892	0.242	0.22308
Table B-13							
(cases)	Never	0.00198	0.00120	0.00206	0.00524	0.05229	0.04705
	Ever	0.00769	0.00331	0.00559	0.01659	0.09178	0.07519

[1] (4) = (1) + (2) + (3)
[2] (6) = (5) - (4)

250103276

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-16. Observed ratios of female former smokers to ever-smokers in the U.S.A., U.K., and Sweden: populations or controls (numbers or %)

Study	Time Frame	Never-Smokers	Current Smokers	Former Smokers	Ever-Smokers	Former/Ever-Smokers
Hammond (1966)	1960	381,369	150,017	31,285	181,302	0.17
Buffler et al. (1984)	1978	41%	38%	21%	59%	0.36
Wu et al. (1985)	1980	92	73	55	128	0.43
Lee (1987b)	1980	48.3%	33.6%	18.1%	51.7%	0.35
Brownson et al. (1987)	1980	47	11	8	19	0.42
Britten (1988)	1982	767	558	320	878	0.36
Humble et al. (1987)	1982	162	63	48	111	0.43
Svensson et al. (1989)	1984	120	53	36	89	0.40
Garfinkel and Stellman (1988)	1982	350,650	132,366	136,909	269,275	0.51

Assumed Ratios by Years (non-traditional societies)[1]

Year	1960	1965	1970	1975	1980	1985
Ratio	0.17	0.23	0.28	0.34	0.39	0.45

[1] Traditional societies (Japan, Greece, China, Hong Kong) are estimated to lag these ratios by about 20 years, although there are no data in the studies to confirm this. However, because the bias for the traditional societies is very low, changes in values of this parameter have little effect.

2501032277

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table B-17. Observed ratios of current smoker lung cancer risk to ever-smoker risk for females

Study	Exposed Cases Plus Controls	Lung Cancer RR: Current Smoker	Lung Cancer RR: Ever-Smoker	Ratio: Current Smoker RR/ Ever-smoker RR
Alderson et al. (1985)	901	4.5	4.75	0.95
Buffler et al. (1984)	701	7.9	6.9	1.15
Garfinkel and Stellman (1988)	832	12.7	8.35	1.52
Humble et al. (1985)	268	18.0	13.0	1.38
Svensson et al. (1989)	261	8.46	6.10	1.39
Wu et al. (1985)	317	6.5	4.4	1.48
Overall	3,280	8.05	6.52	1.24[1]

[1] The summary ratio of 1.24 is the log mean of the individual ratios weighted by the exposed cases plus controls in that study.

05/21/92
2501032278

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

APPENDIX C

REVIEW FORMAT FOR CASE-CONTROL STUDIES

PART I GENERAL

Study name_____

Location_____

Time period (data collection)_____

Study objective(s)_____

_____

_____

The source of the primary data set is the current study _____ or a parent study

(ref)_____

containing CS (current)_____ FS (former) _____ NS (never-smoker) _____

Study uses term "nonsmoker" _____ or "never-smoker" _____ to mean

nonsmoker_____

_____

never-smoker_____

_____

"Exposed" to ETS means (preferably in terms of spousal smoking)

_____

_____

Recall span (how far back in time ETS-exposure was measured)_____

_____

ETS sources include cigarette _____ cigar _____ pipe _____ other _____

2501032279

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Describe inclusion of non-smoking (never smoking) females not currently married (number of cases and controls, assumptions exposure)

_____

_____

_____

II DATA COLLECTION (includes NS_____ FS_____ CS_____ unless noted)

Inclusion/Exclusion criteria

Cases_____

_____

_____

Controls (include matching variables in PART V)_____

_____

_____

Main source of subjects	Cases	Controls
Hospital(s) #_____	_____	_____
Community	_____	_____
Other_____	_____	_____

Incident cases Y_____ N_____

Control sampling

Cumulative _____ Density _____

Unmatched _____ Matched _____

Method of collection	Cases	Controls
Face-to-face	_____	_____
Telephone	_____	_____
Self-admin. ques.	_____	_____
Medical records	_____	_____
Vital stat. records	_____	_____
Other_____	_____	_____

Collected data verified/corroborated with other sources Y_____ N_____

2501032280

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

	Cases	Controls
Sample size (prior to attrition)		
females	_____	_____
males	_____	_____
Attrition (selection or follow-up)		
females	_____	_____
males	_____	_____
Source of response		
subject	_____	_____
proxy	_____	_____

Exposure sources NS_____ FS_____ CS_____

	Yes	No
Childhood	_____	_____
Adulthood	_____	_____
Spouse	_____	_____
Parents/in-laws	_____	_____
Other family/ live-ins	_____	_____
Workplace	_____	_____
Other	_____	_____

Age NS_____ FS_____ CS_____

Distribution	Cases	Controls
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
Mean	_____	_____
Standard error	_____	_____
Standard deviation	_____	_____
Range	_____	_____

PART III CLINICAL DATA

Primary lung cancer verified by NS_____ FS_____ CS_____

Histology	_____
Cytology	_____
Radiology/clinical	_____

2501032281

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Death certificate _____
Tumor registry _____
Mortality records _____
Other_____ _____
Not verified _____

Airway proximity (no. exp cases/no. cases) NS_____ FS_____ CS_____
Central _____
Table_____
Peripheral _____

Tumor type (no. exp cases/no. cases) NS_____ FS_____ CS_____
Squamous cell _____
Table_____
Small cell _____
Adenocarcinoma _____
Large cell _____
Others or unspecified _____

PART IV STATISTICAL ANALYSIS (includes NS_____ FS_____ CS_____ unless noted)

Raw data (for analysis)		Cases	Controls
females	unexp	_____	_____
	exp	_____	_____
males	unexp	_____	_____
	exp	_____	_____

Comments (include measure of exposure) Table _____

250103282

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Unadjusted (crude) analysis

Estimate OR _____ _____% CI (_____,_____)

Comments Table _____

Test of signif p-value _____

Test for trend p-value _____

Comments Table _____

Adjusted analysis

Estimate OR _____ _____% CI (_____,_____)

Test of signif p-value _____

Test for trend p-value _____

Comments Table _____

PART V DEPENDENT VARIABLES (potential confouders and effects modifiers considered)

	In Matching	In Analysis	Otherwise
Age			
Gender			
Race/ethnicity			
Hospital			
Residence/ neighborhood			
Housing type			
House/room sizes			
Vital statistics			
Smoking status			
SES			
Medical health			
Menstrual/ reproductive			
Occupation			
Outdoor air pollution			
Cooking habits			
Drinking			
Diet			

250103228

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Education			
Family history of LC			
Other indoor smoke/fumes			
Radon			
Lifestyle			
Climate/ ventilation			

2501032284

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

APPENDIX D. LUNG CANCER MORTALITY RATES ATTRIBUTABLE TO SPOUSAL ETS IN INDIVIDUAL EPIDEMIOLOGIC STUDIES

Many of the epidemiologic studies on lung cancer and environmental tobacco smoke (ETS) were part of larger investigations that included ever-smokers and never-smokers. For those studies, the lung cancer mortality rate (LCMR) for all causes, appropriate to the location and time period of the study, has been obtained from other sources. Those values and parameter estimates from the studies are used to partition the excess LCMR from all causes (i.e., the excess after allowance for baseline sources) into components attributable to ever-smokers (from current and former smoking) and never-smokers (from exposure to spousal ETS) and to estimate the LCMR in the subpopulations of interest--unexposed never-smokers (meaning not exposed to spousal smoking), exposed never-smokers (exposed to spousal smoking), and ever-smokers ("exposed" is not used to mean exposure to non-spousal ETS, which applies to the whole target population). The method is explained in Sections 6.3.1 and 6.3.2.

Lung cancer mortality rates for the case-accrual periods of case-control studies are displayed in Table D-1. For the studies that collected data on both ever-smokers and never-smokers, the parameter estimates used are shown in Table D-2. The value for the lung cancer mortality rate is from Table D-1, and the remaining estimates are from individual study data. For HIRA(Coh), the lung cancer mortality rate for the time and location of the nested case-control study HIRA is used. For GARF(Coh), the rate for GARF in 1971 is assumed, which is the approximate time of the cohort follow-up. These values may not be very "representative" for lung cancer mortality in these two cohort studies because they extended over several years, and the LCMRs changed from year to year, particularly in the United States. This same difficulty arises in choosing a "representative" year for lung cancer mortality in the case-control studies, although to a lesser degree. The most extreme examples are KABA, PERS, INOU, and GARF with case-accrual periods of 10 years or more.

The estimates of prevalence of ever-smokers and the percent of never-smokers exposed to spousal smoking are the observed proportions in the control group. The extent to which the control group is representative of the country's population differs between studies, with those most questionable shown in Table 5-14A. The study reviews in Appendix A provide more detailed information. The restriction of cell types among cases in some studies is another consideration. Active smoking is much more strongly associated with occurrence of squamous and small cell carcinoma than with large cell carcinoma and adenocarcinoma. FONT presents evidence that passive smoking is more associated with adenocarcinoma than with other cell types. As noted

250103285

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

in Table 5-15, some studies excluded candidate lung cancer cases of specific histopathological types. This may produce some bias and distortion of comparison between studies. For example, BROW includes only cases of adenocarcinoma, which should bias the relative risk of ever-smokers toward unity, thus attributing too little lung cancer mortality to active smoking and too much to passive smoking and background sources.

Of a more positive nature, there is some advantage to using data from a single study to assign attributable *fractions* to different causes. To estimate the yearly number of lung cancers from each cause, the fraction is multiplied by the LCMR for the location and time of the study; that figure has to be obtained from sources on vital statistics. As seen in Table D-2, the mortality rates from lung cancer vary considerably between and within countries. For example, the rates used for studies in the United States range between 9 and 26. Applying the lung cancer rate suitable to each individual study should provide better estimates for comparison within a country than using a single figure for the whole country for some specific year.

Despite the reservations described, partitioning the lung cancer mortality for each study into components attributable to ever-smoking, spousal ETS, and baseline sources (nontobacco smoke and nonspousal ETS) provides a broad overview worth noting. The calculated values are shown in Table D-3. Estimates of relative risk for exposure to spousal ETS (RR_2 in notation of Section 6.3.2) less than 1.0 (see Table 5-8) were replaced by 1.0 to avoid a negative LCMR attributable to spousal ETS and the consequent inflation of the LCMR attributable to baseline sources and ever-smoking. Aside from the studies for Hong Kong and China, estimates of lung cancer mortality due to background sources cluster in the interval 1.5 to 5.5 (excluding BROW, which is strongly biased), predominantly from 3 to 5. The values for Hong Kong and China, however, are much higher, ranging from 7 to 14.5. The presence of indoor sources of non-ETS encountered in some of the studies in China may be a factor, but there is no apparent explanation for the outcome in Hong Kong. Assuming that the background rate of lung cancer is much higher in Hong Kong (and possibly China) as it appears, then the question arises as to whether the high excess rate relative to other countries may be attributable to higher exposure to ETS aside from spousal smoking or whether it is more likely due to other causes. Summary data from the ten-country collaborative study of ETS exposure to nonsmoking women conducted by the International Agency for Research on Cancer (IARC) (Riboli et al., 1991) was kindly submitted to us for Hong Kong, Japan (Sendai), and the United States (Los Angeles, New Orleans) from Drs. L.C. Koo, H. Shimizu, A. Wu-Williams, and T.H. Fontham, respectively. The average cotinine/creatinine (ng/mg) levels for nonsmoking women who are not employed and not married to a smoker are close for Sendai, Los Angeles, and New Orleans, but they are several times higher

250103228

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

for Hong Kong. Consequently, a high contribution to background lung cancer mortality from ETS aside from spousal smoking cannot be eliminated as a factor.

The lung cancer attributable to ever-smoking, spousal smoking, and baseline sources depends on the population proportions for those categories as well as the relative risks. Study estimates of the LCMR in each category, in units of lung cancer deaths per 100,000 at risk per year, are shown in Table D-4. The last two columns show the ratios of the LCMR and the excess LCMR for exposed never-smokers to ever-smokers. As above, relative risk estimates of less than 1.0 were set to 1.0 for the calculations. There is considerable variability across study estimates, even within the same country, as observed previously in the relative risks for spousal smoking.

To summarize, for studies that included data on ever-smokers, the LCMR for all causes was partitioned by attributable source (Table D-3). Although there is considerable uncertainty in the estimates from statistical variability and other sources, the outcomes provide some useful gross comparisons. For example, the lung cancer mortality rates from all causes differ markedly between countries and also vary widely between studies within the United States. The proportion of lung cancers attributable to ever-smoking is very high in the United States, compared to some more traditional countries (e.g., Japan and Greece).

Individual study estimates of the number of lung cancer deaths per year per 100,000 of female population from exposure of never-smokers to spousal ETS are predominantly between 0 and about 2.5. Estimates of the LCMR attributable to baseline sources (nonspousal ETS and nonsmoking causes) are somewhat higher, largely between 2 and 5, except in Hong Kong and China, where they range between 7+ and 14. (The U. S. study denoted as BROW has a high value, but that should be upwardly biased because it used only cases of adenocarcinoma, which is not a common cell type in smokers.) For reasons discussed in Chapter 5, we would be reluctant to draw conclusions about China on the basis of the epidemiologic studies. The evidence from Hong Kong, however, is very suggestive that the lung cancer rate in women due to baseline sources is very high. The extent to which that is attributable to nonsmoking sources of lung cancer and/or high exposure to nonspousal ETS is not apparent. The cotinine data for Hong Kong from the ten-country IARC study (Riboli, 1990) is consistent with excessively high ETS exposure, so nonspousal ETS may be a factor.

2501032287

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table D-1. Female lung cancer mortality from all causes in case-control studies[1]

Study	Location	Case Accrual	Begin	Average	End	Accrual -10 yrs Average	Accrual -20 yrs Average
AKIB	Japan	1971-80	5.13	6.05	7.08	4.57	2.30
BROW	USA	1979-82	15.68	17.29	19.09	9.49	4.75
BUFF	USA	1976-80	13.94	15.29	17.20	7.86	4.38
CHAN	HK	1976-77	23.59	23.59	23.59	19.05	*
CORR[2]	USA	1979-82	26.0	26.0	26.0	9.49	4.75
GAO[3]	China	1984-86	*	18.0	*	14.3[2]	5.1[2]
GARF	USA	1971-81	9.45	13.55	17.20	6.87	*
GENG[3]	China	1983	*	27.8	*	13.8[2]	*
HIRA[7]	Japan	1965-81	4.46	5.70	7.08	4.01	*
HUMB[2]	USA	1980-84	17.7	17.7	*	10.55	5.13
INOU	Japan	1973-83	5.55	6.53	7.46	4.93	2.95
JANE[2]	USA	1982-84	23.7	23.7	*	9.06	5.42
KABA[4]	USA	1961-80	4.69	13.20	17.20	6.61	4.16
KALA[4]	Greece	1987-89	6.58	6.58[4]	6.58	6.75	5.83[4]
KATA[4]	Japan	1984-87	*	7.46[4]	*	4.66	2.26
KOO	HK	1981-83	22.34	22.61	22.75	19.82	*
LAMT[4]	HK	1983-86	22.75	23.46	23.69	21.33	*
LAMW	HK	1981-84	22.34	22.88	23.69	20.09	*
LEE	Eng/Wal	1979-82	16.28	17.11	17.89	12.60	8.1
PERS[4]	Sweden	1961-80	3.71	5.09	7.56	3.95[4]	*
SHIM[4]	Japan	1982-85	7.46	7.46[4]	7.46	5.65	4.28
SOBU[4]	Japan	1986-88	7.46	7.46[4]	7.46	6.36	4.93
SVEN[4]	Sweden	1983-85	7.72	7.72[4]	7.72	5.78	3.80
TRIC	Greece	1978-80	6.88	6.40	5.99	5.75	5.31[5]
WU	USA	1981-82	17.20	18.15	19.09	10.14	4.96
WUWI[6]	China	1985-87	*	11.6	*	9.2[2]	*

[1] Rates are per 100,000 per year. Annual rates for 2-year periods from Kurihara et al. (1989) were averaged over the years cases were accrued for each study unless otherwise noted. Where part (or all) of the accrual period fell 1 or 2 years outside the years for which rates were available, rates from the nearest 2-year period available were assumed to apply to the missing years. U.S. rates are for white females only.

[2] Data for accrual period from 1978-82 rates in IARC (1987), standardized to 1950 world population from Kurihara et al. (1989). For Correa, weighted average of white and black rates; for Humble, weighted average of Hispanic and non-Hispanic white rates.

250103288

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table D-1. (continued)

[3] Accrual period data for Gao and Geng derived from IARC (1987) by standardizing to same 1950 world population used by Kurihara et al. (1989). Gao rates are for 1978-82; Geng, 1981-82. For -10 years, Gao and Geng are 1973-75 rates standardized to the 1960 world population from China Map Press (1979). Gao -20 years value is nonadjusted 1961 rate from Kaplan and Tsuchitani (1978).

[4] Where rates for the period were not available in Kurihara et al. (1989), substitutions were made as follows: Kalandidi from 1984-85 rates; Kabat 1982-83; Katada 1982-83; Lam, T. 1984-85; Pershagen 1952-53; Shimizu 1982-83; Sobue 1982-83; Svensson 1982-83.

[5] World-standardized rate for 1961-65 from Katsouyanni et al. (1990). [In Greek: translation provided by Trichopoulos.]

[6] Accrual period value estimated by multiplying LCMR in Shanghai for period 1978-82 (standardized to the 1950 world population) by the ratio of LCMRs in Liaoning and Heilonjiang to Shanghai, for the period 1973-75 (standardized to the 1960 world population). Data are from China Map Press (1979). Value for -10 years is the 1973-75 rate.

[7] The nested core-control study of Hirayama.

* Data not available.

250103289

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table D-2. Parameter values used to partition female lung cancer mortality into component sources[1]

Case-Control	Lung Cancer Mortality	Ever-smokers		Never-smokers	
		Prevalence (%)	Relative Risk	Percent Exposed (%)	Relative Risk
AKIB	6.05	21	2.38	70	1.50
BROW	17.29	29	4.30	15	1.50
BUFF	15.29	59	7.06	84	0.81
CHAN	23.59	26	3.48	47	0.74
CORR	26.00	47	12.40	46	1.90
GAO	18.00	18	2.54	74	1.19
GARF(Coh)	9.45	33	3.50	72	1.15
GENG	27.80	41	2.77	44	2.16
HIRA	5.70	16	3.20	77	1.53
HIRA(Coh)	5.70	16	3.20	77	1.37
HUMB	17.70	41	16.30	56	1.98
INOU	6.53	16	1.66	64	2.55
KABA	13.20	42	5.90	60	0.74
KALA	6.58	17	3.32	60	1.92
KOO	22.61	32	2.77	49	1.54
LAMT	23.46	24	3.77	45	1.64
LAMW	22.88	22	4.12	56	2.51
LEE	17.11	60	4.61	68	1.01
SOBU	7.46	21	2.81	54	1.13
SVEN	7.72	43	5.97	66	1.19
TRIC	6.40	11	2.81	52	2.08
WU	18.15	58	4.38	60	1.31
WUWI	11.60	37	2.24	55	0.78

[1] For studies with data on both ever-smokers and never-smokers. Table entries are drawn from Tables 5-4, B-8 and D-1, which contain explanatory footnotes.

05/15/92
250103229O

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table D-3. Female lung cancer mortality rates by attributable source[1]

Study	Location	Baseline Sources[2] No.	Baseline Sources[2] %	Spousal Smoking No.	Spousal Smoking %	Ever-smoking No.	Ever-smoking %
AKIB	Japan	3.47	57	0.96	16	1.61	27
BROW	USA	8.22	48	0.44	3	8.63	50
BUFF	USA	3.34	22	0.00	0	11.95	78
CHAN	HK	14.34	61	0.00	0	9.25	39
CORR	USA	2.89	11	0.63	2	22.47	86
GAO	China	12.36	69	1.42	8	4.22	23
GARF (Coh)	USA	4.67	49	0.33	4	4.44	47
GENG	China	10.67	38	3.21	12	13.92	50
HIRA (Coh)	Japan	3.28	58	0.78	14	1.63	29
HUMB	USA	1.57	9	0.51	3	15.62	88
INOU	Japan	2.97	45	2.47	38	1.09	17
KABA	USA	4.32	33	0.00	0	8.88	67
KALA	Greece	3.04	46	1.39	21	2.15	33
KOO	HK	11.41	50	2.05	9	9.14	40
LAMT	HK	10.94	47	2.39	10	10.12	43
LAMW	HK	7.35	32	4.85	21	10.68	47
LEE	Eng./Wales	5.37	31	0.01	0	11.73	69
SOBU	Japan	5.05	68	0.28	4	2.13	29
SVEN	Sweden	2.19	28	0.16	2	5.37	70
TRIC	Greece	3.42	53	1.71	27	1.27	20
WU	USA	5.17	28	0.40	2	12.58	69
WUWI	China	7.95	69	0.00	0	3.65	31

[1] Rates are per 100,000 per year. Data not available for GARF, JANE, PERS, SHIM, BUTL(Coh), and HOLE(Coh).

[2] Nonspousal ETS and non-ETS sources.

2501032291

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

Table D-4. Lung cancer mortality rates of female ever-smokers (ES) and never-smokers (NS) by exposure status[1]

Study	Location	(1) Unexposed NS[2]	(2) Exposed NS[3]	(3) E.S.	(2) As a Percentage of (3)	(2) - (1) As a Percentage of (3) - (1)
AKIB	Japan	3.47	5.21	11.16	47	23
BROW	USA	8.21	12.32	37.99	32	14
BUFF	USA	3.34	3.34	23.59	14	0
CHAN	HK	14.34	14.34	49.91	29	0
CORR	USA	2.89	5.49	50.70	11	5
GAO	China	12.35	14.70	35.79	41	10
GARF (Coh)	USA	4.67	5.37	18.12	30	5
GENG	China	10.66	23.03	44.62	52	36
HIRA (Coh)	Japan	3.28	4.49	13.49	33	12
HUMB	USA	1.57	3.11	39.66	8	4
INOU	Japan	2.96	7.56	9.80	77	67
KABA	USA	4.32	3.78	25.46	17	0
KALA	Greece	3.04	5.84	15.66	37	22
KOO	HK	11.41	17.57	39.98	44	22
LAMT	HK	10.94	17.94	53.12	34	17
LAMW	HK	7.35	18.45	55.89	33	23
LEE	Eng/Wal	5.36	5.42	24.91	22	0
SOBU	Japan	5.05	5.70	15.18	38	6
SVEN	Sweden	2.18	2.60	14.69	18	3
TRIC	Greece	3.41	7.10	14.99	47	32
WU	USA	5.16	6.77	26.85	25	7
WUWI	China	7.95	7.95	17.81	45	0

[1] Rates are per 100,000 per year. Data not available for GARF, JANE, PERS, SHIM, BUTL(Coh), and HOLE(Coh).

[2] Exposed to baseline sources--nonspousal ETS and non-ETS sources.

[3] Exposed to baseline sources plus spousal ETS.

2501032292

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

APPENDIX E. STATISTICAL FORMULAE

E.1. CELL FREQUENCIES

The observed outcome of a case-control study or a cohort study may be depicted in a 2 x 2 table, where a, b, c, and d are cell frequencies.

		ETS Exposed: Yes	ETS Exposed: No
Lung Cancer Present	Yes	a	b
	No	c	d

E.2. CASE-CONTROL STUDIES

The true (but unknown) odds ratio is estimated by the observed odds ratio (OR),

$$OR = ad/bc.$$

A confidence interval on the (true) odds ratio may be calculated from the normal approximation to the distribution of log(OR), the natural logarithm of OR (Woolf, 1955). The variance of log(OR) is estimated by

$$Var(\log(OR)) = 1/a + 1/b + 1/c + 1/d$$

and the standard error by its square root,

$$SE(\log(OR)) = (Var(\log(OR)))^{1/2}.$$

Approximate 90% confidence limits are given by

$$\log(OR) \pm 1.645\ SE(\log(OR)).$$

The value 1.645 is replaced by 1.96 for 95% confidence limits and, in general, by $Z_{\alpha/2}$ for 100(1 - α)% confidence limits. The confidence bounds obtained in this way are sometimes called *logit limits* (Breslow and Day, 1980; p.134). Significance level (P-value) of a test for effect, i.e., H_o: (true) odds ratio = 1 against the alternative H_a: (true) odds ratio > 1, is the area under the standard normal curve to the right of the value of the *test statistic*, given by log(OR)/SE(log(RR)).

250103293

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

If the (true) odds ratios are assumed to be equal in k studies, then a pooled estimate is calculated from

$$\log(OR(P)) = \sum w_i \log(OR)_i / \sum w_i$$

where the summations are on i, from 1 to k; OR(P) is the pooled estimate; $\log(OR)_i$ is the logarithm of OR from the ith study; and $w_i = (Var(\log(OR)_i))^{-1}$ is the *weight* of the ith study (Breslow and Day, 1980).

E.3. COHORT STUDIES

The true (but unknown) relative risk is estimated by the observed relative risk (RR),

$$RR = (a/a+c)/(b/b+d).$$

A confidence interval on the (true) relative risk may be calculated from the normal approximation to the distribution of log(RR), using the analogue of Woolf's method referred to above (Katz et al., 1978). The variance of log(RR) is estimated by,

$$Var(\log(RR)) = c/(a^2 + ac) + d/(b^2 + bd)$$

and the standard error by its square root,

$$SE(\log(RR)) = (Var(\log(RR)))^{1/2}.$$

The remaining calculations follow the description for case-control studies in Section E.2 with "odds ratio" and "OR" replaced by "relative risk" and "RR," respectively. The pooled estimate of relative risk from both case-control and cohort studies is calculated by the same methodology for pooling estimates from case-control studies or from cohort studies separately, i.e., the logarithm of each individual estimate is weighted inversely proportional to its estimated variance (Kleinbaum et al., 1982).

☆ U.S. GOVERNMENT PRINTING OFFICE: 1992— 650- 572

25010322 94 05/15/92

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000

United States
Environmental Protection
Agency

Center for Environmental Research
Information
Cincinnati, OH 45268

BULK RATE
POSTAGE & FEES PAID
EPA
PERMIT No. G-35

2501032295

Official Business
Penalty for Private Use, $300

Please make all necessary changes on the above label, detach or copy, and return to the address in the upper left-hand corner.

If you do not wish to receive these reports CHECK HERE ☐: detach, or copy this cover, and return to the address in the upper left-hand corner.

EPA/600/6-90/006B

Source: https://www.industrydocuments.ucsf.edu/docs/sfhl0000